Modern imaging: its role in prediction of outcome after stroke and TIA

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Appendixes

List of figures and tables

Declaration

I, Shelagh B. Coutts, hereby certify that:

a. this thesis has been composed entirely by myself

b. that the work contained herein is my own work*, excepting those areas where the help of others is acknowledged

c. that I undertook the work contributing to this thesis whilst employed in the Department of Clinical Neurosciences at the University of Calgary, CANADA and

d. that I have not submitted this thesis in candidature for any other degree, postgraduate diploma or professional qualification.

Signed...

Date.....4/9/2005.....

* The thesis is based upon a collaborative study, the VISION project, which involved various clinicians, statistical, computing and administrative staff. My specific contribution to the study is outlined in Appendix 11.

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Abstract

Background: The acute treatment of stroke and transient ischaemic attack (TIA) is changing and imaging is central to the diagnosis and treatment of these patients. The hypothesis of this study is that simple CT and MRI baseline characteristics can be reliably acquired in acute ischemic stroke patients and can be used to predict clinical outcome in acute stroke patients, minor stroke patients and TIA patients.

Methods: In a cohort of acute ischemic stroke and TIA patients we looked at the reliability of imaging parameters and how they related to clinical outcome. We tested the hypothesis that the Alberta Stroke Program Early CT Score (ASPECTS) is reliable in real time and that using the ASPECTS scale to assess CT angiography source images would better predict final infarct than CT alone. We also assessed the reliability of quantifying mismatch between DWI and PWI on MRI with the human eye. We also hypothesized that we could predict which minor stroke (NIHSS$\leq$ 3) and TIA patients would have recurrent clinical or MRI events using a combination of base line diffusion weighted MRI (DWI), perfusion weighted MRI (PWI) and MR angiography techniques.

Results: Inter-observer agreement between real time and expert ASPECTS was substantial; κw=0.69 (95%CI 0.59-0.79). Using a follow up ASPECTS as the final infarct size, we found that CTA-SI gives a more accurate estimate of tissue that is at risk of infarcting than does a NCCT alone. Visual assessment of DWI-PWI mismatch had an inter-rater reliability of 0.68 (95% CI: 0.52 to 1.0; SEM=21.6%) and an intra-rater reliability of 0.80 (95% CI: 0.47 to 1.0; SEM=16.9%).

The 90-day risks, adjusted for baseline characteristics of minor stroke and TIA patients having a recurrent clinical event, were 4.3% (no DWI lesion), 10.8% (DWI lesion, no vessel occlusion), and 32.6% (DWI lesion and vessel occlusion), respectively (p=0.02). The percentages of patients who were functionally dependent at 90 days in the three groups were; 1.9%, 6.2% and 21.0% respectively (p=0.04). 9.8% (CI_{95} 5.5-15.9) of minor stroke and TIA patients had MR evidence of recurrent lesions on their MRI at 30days. Increasing lesion number at baseline was associated with recurrent imaging events. We identified that 34% of TIA patients show evidence of perfusion abnormalities on an acute MRI.

Discussion: We found that non contrast CT ASPECTS was reliable when applied in real time. CTA-SI ASPECTS has a greater sensitivity to ischaemic changes and more accurately identifies the volume of tissue that will ultimately infarct compared to non contrast CT alone. We found that quantifying DWI-PWI mismatch using the human eye is reproducible, but not consistent among observers. The margin of error between raters was large and this may compromise its use for clinical trial enrollment. The presence of a DWI lesion and a vessel occlusion on an MRI among patients presenting acutely with a TIA or minor stroke is predictive of an increased risk of a future stroke and of subsequent functional dependence. Minor stroke and TIA are associated with a 10% risk of new lesions on MRI and the risk of new lesions was increased with increasing number of baseline lesions. A high proportion of TIA patients show a perfusion abnormality despite having their neurological symptoms completely resolved. Further work is needed on larger populations of patients to see if the imaging abnormalities identified in this work are predictive of clinical outcome and to see if these results can be replicated.

1. Chapter 1: INTRODUCTION and LITERATURE REVIEW

Ischaemic stroke is currently the fourth leading cause of death in Canada and leading cause of adult disability.[1] In a developed country, the annual incidence of first stroke is 1800 per 1 million population, while the incidence of transient ischaemic attacks (TIA) is 500 per 1 million.[2,3,4,5,6] Despite this being a common disease with devastating consequences there currently is a tremendous lack of effective acute treatment interventions for iscaemic stroke and TIA patients. Numerous neuroprotective agents have been studied in clinical trials, but none have proven efficacious. Intravenous tissue plasminogen activator (tPA) remains the only drug and route of administration approved in North America for acute stroke treatment based on the results of the NINDS tPA trials[7] and is recommended in all disabling ischaemic stroke patients fulfilling the clinical criteria of the NINDS tPA study.[8] Eight stroke patients must be treated to "cure" one additional patient of any residual clinical disability. The narrow therapeutic time window of under three hours from symptom onset, has limited the utility of this therapy in clinical practice. A recent evaluation of tPA use in Medicare patients in the United States revealed only 1.7% of all strokes were treated with this therapy.[9] Efforts to improve pre-hospital delivery systems can have some impact on percentage treated but the vast majority of ischaemic stroke patients will never be eligible based on current inclusion criteria.[10] Work has shown that for a variety of reasons, for every one patient treated with tPA, 11 patients are excluded from therapy even if they present within 3 hours of onset. At foothills medical centre it was identified that 27% of stroke patients arrived in the emergency department within three hours from symptom onset. However a majority of these <3 hour stroke patients were excluded from therapy because symptoms were deemed too mild (13.1%) or patient was felt to be clinically improving (18.2%).

Tragically, a significant percentage of these patients deteriorated in hospital resulting in dependence or death.[12] Transient ischaemic attack (TIA) patients are at particularly high risk for recurrent disabling ischaemic events (5% within 48 hours) early after symptom onset yet there is no reliable method of identifying or preventing such events.[13]

Ischaemic stroke and TIA is a heterogeneous disease with many factors influencing outcome. New approaches are needed to target a larger population of stroke and TIA patients with the aim to prevent recurrent events and limit disability. Recently several senior stroke experts urged the further development of neurovascular imaging to further refine the population of patients that can be treated.[14] Stroke clinical trials to date have largely ignored the potential of neurovascular imaging to best identify appropriate target populations. Neurovascular imaging techniques offer such hope by providing a "window" to the ischaemic brain and intracranial vasculature. Clinical factors such as age, gender, stroke severity and vascular risk factors alone have proven limited in predicting outcome.[15]

1.1. Mechanisms of Ischaemic Stroke and Transient Ischemic Attack's

Approximately 95% of ischemic stroke and TIA's are caused by small vessel disease, cardioembolism and atheroembolic events.[16] Finding a cause for the ischaemic stroke is important since it allow any potential causes to be treated. For example atrial fibrillation is a common and important cause of cardioembolic stroke since it is treatable with anticoagulation; internal carotid artery stenosis is an important cause if atheroembolic events and again is potentially treatable with

carotid endarterectomy. Small vessel disease generally causes "lacunar" syndromes which are caused by disease of the small intracranial perforating arteries. Cardioembolic strokes are caused by a variety of different sources including atrial fibrillation, infective endocarditis, prosthetic heart valves and recent myocardial infarction.

1.1.1. Pathophysiology of ischemic stroke

The pathophysiology of acute ischemic stroke involves an event that causes a reduction in cerebral blood flow and then the changes that arise at a molecular level as a result of the ischemia. The molecular changes leads ultimately lead to ischemic necrosis (infarction). Ischemic necrosis is a complicated process that is not completely understood. However, certain components are clear; huge increases in intracellular calcium occur, together with free radicals and acidosis.

1.1.2. Physiology of cerebral blood flow

The human brain uses glucose as its only substrate for energy metabolism and requires a constant supply of oxygenated blood containing a constant supply of glucose to maintain normal function. In normal brain, blood flow is closely coupled with metabolic demand. If the brain becomes damaged then blood flow and metabolism become uncoupled and so normal flow does not now necessarily imply normal metabolism and function. Under normal circumstances, cerebral blood flow

is maintained at a relatively constant level, irrespective of the cerebral perfusion pressure. This is called autoregulation. When the brain has been damaged by ischemia, autoregulation is less effective and CBF more closely follows changes in systemic arterial pressure. This is important in mild ischemia, where reductions in CBF from above 20ml/100g/min which is sufficient to sustain brain function, to lethal levels below 10ml/100g/min[17].

When cerebral perfusion pressure falls, intracranial arteries dilate to maintain cerebral blood flow. This results in an increase in cerebral blood volume (CBV). When vasodilatation is maximal, further falls in perfusion pressure result in a fall in the CBF:CBV ratio and an increase in the oxygen extraction fraction to maintain tissue oxygenation. When the oxygen extraction fraction is maximal, further falls in perfusion pressure lead to a reduction in the cerebral metabolic rate of oxygen and the symptoms of cerebral ischemia.

1.1.3. Penumbra and critical flow thresholds

As cerebral blood flow drops, a critical threshold is reached where the normal electrical activity of neurons is suppressed. If blood flow continues to fall further then another threshold is reached when cell necrosis begins[18]. Cells in between these 2 states are considered to be in the "ischemic penumbra" - i.e. they may not be functioning, but they are still alive and could either survive or die[19,20]. The ischemic penumbra can be defined as an area of severely ischemic, functionally impaired, but surviving brain tissue which is at risk of infarction but can be saved, if it is

reperfused before it is irreversibly damaged.[21] If no reperfusion occurs then the penumbra will be progressively recruited until the maximum infarct is reached.

When the CBF falls to below about 20mL/100g of brain per minute the neuronal electrical activity ceases and the first threshold is reached[22]. When blood flow falls to about 10ml/100g of brain per minute this is the beginning of irreversible cell damage. This is the point at which membrane failure occurs[23].

1.2. Thrombolysis outside the 3 hours time window- "the tissue window"

Most ischaemic stroke patients are not eligible for tPA because they arrive after the three hour window.[8] However, due to the experimental evidence described above regarding the ischemic penumbra there is much discussion regarding use of imaging characteristics rather than time as a barrier to treatment. There is increasing clinical evidence that these "late" patients may still derive benefit from thrombolysis at later time points.[24,25,26] Angioplasty and stenting of critical carotid artery narrowing has been associated with dramatic clinical improvement more than 10 hours after symptom onset.[27] Numerous reports of dramatic clinical improvement have been identified in patients with basilar artery occlusion, who are treated with intra-arterial thrombolysis at late time points. These are patients with acute cerebral ischaemia in whom brain tissue is at risk of infarction but permanent damage has not yet occurred. Depth of ischaemia and length of ischaemia are both critical in determining when and how much brain will infarct after cerebral vascular occlusion[28]. Patients with strokes are heterogeneous and the interactions of multiple variables will in turn affect the depth of ischaemia or the susceptibility of tissue to

damage (e.g. site of occlusion, collateral supply, blood pressure, body temperature, glucose and age)[29]. In addition, different tissues within the brain, e.g. grey and white matter, cortex and subcortex, have different thresholds of ischaemia at which infarction is inevitable[30]. The challenge, in the clinical setting, is to find surrogate markers that reflect the degree of ischaemia and to therefore identify patients with a baseline "tissue window" (tissue at risk which has not yet infarcted) that allows intervention. This would allow the treatment of a large number of ischaemic stroke patients who currently are ineligible for thrombolysis because they are beyond the "magical" 3 hour time window. Thrombolysis carries with it a risk of hemorrhage and may be more of an issue when attempting to prolong the window for thrombolysis. New research has examined some of the MR parameters associated with hemorrhage.[31] A recent study of patients awakening with symptoms identified that 10% had significant regions of ischaemic tissue at risk based on MRI parameters which could represent a patient population which is salvageable with intervention.[32] Studies such as these allow us to further refine the target population for thrombolysis.

1.3. Minor Stroke and TIA

Time is critical to the diagnosis and management of cerebrovascular disease[26]. The classical definitions of stroke and transient ischaemic attack (TIA) are arbitrarily set around duration of focal neurological deficit more or less than 24 hours respectively[33]. Ischaemic stroke is a focal neurological deficit of vascular origin in which the deficits last at least 24 hours. By contrast a transient Ischemic Attack (TIA) is a clinical syndrome characterized by an acute loss of focal neurological function of vascular origin. Those with disabling ischaemic stroke presenting within

three hours of onset are eligible for treatment with thrombolysis[7]. Systems of care have been streamlined to maximize the utilization of thrombolysis with the end result that patients with both disabling and non-disabling events are presenting well within the 24-hour window that is required to make the classical definitions[12]. The key question now is how to triage those with non-disabling deficits more effectively.

It has long been realized that a previous TIA or minor stroke confers a higher risk of recurrent stroke[34] with the conclusion drawn by some that the difference between the two is probably redundant.[35,36] The short-term, 90-day, risk of stroke following a TIA is between 10 and 20 percent.[13,37,38] Among patients with mild stroke, deemed too mild for thrombolytic therapy, one third are dependent or dead at hospital discharge.[12] Half of the risk of recurrent stroke is accrued within the first 48 to 72 hours of the event[13], hence the necessary urgency to identify those at immediate risk.

For many years it was presumed that TIA's were associated with complete resolution of brain ischaemia leaving no permanent brain injury.[39,40] However, since the original definitions of TIA and stroke were established, advances in neuroimaging have occurred. A substantial proportion of patients with TIAs, according to the classical definition, have injury observed on diffusion weighted imaging (DWI) of the brain on magnetic resonance imaging (MRI).[41,42,43,44,45] Patients with prolonged duration of ischaemia[44,45] or having speech or motor deficits[42] are more likely to demonstrate injury on brain imaging. However, currently no group has looked to see if perfusion abnormalities are present in TIA patients despite resolution of symptoms. No risk stratification model exists that is specific or sensitive enough to predict those at the highest risk of recurrence. Johnson et al[13]

proposed clinical risk factors including diabetes and age greater than 60 years old, to identify those at the highest risk, but these have not been prospectively validated. They are essentially the same as those that have been proposed previously, which have failed previous validation efforts. [13,46,47] It is therefore not clear how to triage this group of patients accurately, to reflect the risk of recurrence according to their clinical presentation or personal characteristics. Proposed causes of clinical deterioration or recurrent events have been suggested which include: recurrent emboli[48], hemodynamic failure from persistent occlusion of the extracranial[49] or intracranial arteries[50], rethrombosis[51,52,53] or reocclusion.[54] Persistent occlusion and reocclusions of the intracranial and extracranial vessels can be identified by TCD, CTA or MRA. Identifying a high risk group among minor stroke and TIA patients could lead to randomized trials in a new therapeutic target population.

1.4. Non contrast CT and CT bolus techniques

Computed tomography (CT) is currently the modality of first choice for imaging patients with acute stroke. Although magnetic resonance imaging (MRI) has uncovered considerable information on the process of ischaemic infarction, most patients with a stroke present to community hospitals without acutely available MRI [55]. MRI is also prohibited until contraindications can be ruled out. Claustrophobia, motion artifact, longer scan time, inability to use standard treatment or monitoring equipment make MRI a difficult technique to rely upon in a high volume stroke center. Although non contrast CT was initially used to exclude intracranial hemorrhage and other non-stroke pathologies, advanced CT techniques are increasingly recognized as a modality to characterize early signs of ischaemia.[56,57]

Imaging techniques that improve patient selection for acute stroke treatment are vital. With the use of multi-slice CT scanners, the potential information available from a CT scan has increased.[58] CT angiography and CT perfusion techniques can refine the current clinical criteria for patient selection for thrombolysis.[7]

The European Co-operative Acute Stroke Study (ECASS)[59] trials first recognized the importance of assessing the CT scan for early ischaemic changes in an attempt to predict benefit from intravenous thrombolysis. The ECASS I protocol intended to exclude patients with extensive changes of ischaemic cerebral injury on the CT scan, defined as >33% of the MCA territory. Unfortunately the local investigators missed 17.4% of patients with >33% of the MCA territory affected. In these patients there was evidence of large ischaemic change on the CT that had been overlooked by the local investigators. Early ischaemic changes are subtle and the reliability of assessing the extent of CT infarction has been relatively poor.[57,60,61,62] Despite these limitations this method of semi-quantifying early ischaemic changes in the middle cerebral artery territory has been used in future thrombolytic trials to exclude patients with large areas of brain already infarcted.

Non contrast CT (NCCT) findings can predict vascular occlusion and still viable ischaemic brain[63,64]. The Alberta Stroke Program Early CT Score (ASPECTS) was devised by the Calgary stroke program to provide a systematic approach for assessing early ischaemic changes in regions of the middle cerebral artery (MCA) territory[65]. Using this score we achieved good agreement among CT observers (Kappa 0.71-0.89 when the affected hemisphere was known)[66]. By systematically quantifying early CT ischaemia we were able to predict functional outcome and the risk of symptomatic hemorrhage in tPA treated stroke patients[65]. The advantage of

ASPECTS is that it combines a semi-quantitative estimate of volume with localization by simply weighting smaller volumes in the basal ganglia and internal capsule equally with larger volumes of brain designated M1 through M6. Details of ASPECTS scoring is outlined in Pexman et al.[67] Recent work using ASPECTS to retrospectively score the scans from the PROACT-II study (patients randomized within 6 hours of symptoms to intra-arterial thrombolysis with recombinant pro-urokinase or control) showed that ischaemic stroke patients with a baseline ASPECTS > 7 were three times more likely to have an independent functional outcome with thrombolytic treatment compared to control. Patients with a baseline ASPECTS <7 were less likely to benefit from treatment.[56]

Increased density of vascular structures known as hyperdense artery signs have also become valuable in identifying arterial occlusion.[68] The hyperdense middle cerebral artery sign (HMCAS) correlates well with middle cerebral artery (MCA) occlusion based on angiography[69] and the recently described MCA "dot" sign[70] correlates with distal MCA occlusion identified by conventional angiography.[71]

Newer CT bolus tracking techniques including CT angiography and CT perfusion (CTP) also are available but require the use of nonionic intravenous contrast. The sensitivity and specificity of CT angiography is excellent for diagnosing large vessel occlusion.[72] Source images from CT angiography (CTA-SI) can be rapidly obtained with minimal delays after a non-contrast CT (NCCT) in the Emergency Room.[73,74,75] Although CTA has been shown to have value in identifying vessel occlusion, CTA source images (CTA-SI) also have value in the assessment of tissue status. The administration of a single contrast bolus can be used to simultaneously acquire both CT angiographic images (CTA) of the complete

neurovascular system (arch-to-vertex) and whole brain "perfused" blood volume-weighted CTA source images (CTA-SI). "Perfused" reflects the fact that only contrast material that reaches the imaged voxels during scan acquisition contributes to measured blood volume. Thus, although theoretically CTA-SI should be entirely blood volume-weighted, a component of flow weighting may also exist. The bolus is given with timing that should allow visualization of only the arterial phase and not the venous phase. Schramm et al found that the combination of CT, CTA and CTA-SI was comparable to that of an MR-DWI.[76] CTA-SI can also be useful in predicting final infarct volume.[77,78] Brain tissue with a low cerebral blood volume appears hypodense on CTA-SI, thus effectively delineating regions of ischaemia.[77] Currently there are only a few stroke clinical outcome studies using CT angiography and quantitative CTP[79,80] although recent work on a small number of patients suggests that CT perfusion and NCCT can be equivalent to DWI/PWI imaging in identifying potentially salvageable tissue.[81] Further studies are needed in this area.

1.5. Multimodal Magnetic Resonance Imaging (mMRI)

Fast MR imaging is possible in the acute stroke setting. Multi-modal MR imaging can provide information on the status of brain parenchyma, vasculature and cerebral perfusion. Diffusion-weighted imaging (DWI) and the apparent diffusion coefficient (ADC) maps derived from them detect change in the local diffusion of water and are sensitive to changes of hyperacute ischaemia[82]. This sequence analyzes water movement within the brain tissue at the molecular level. With infarction of brain tissue, normal water movement is restricted and this abnormality can be visualized on DWI scan images. The diffusion data can be presented as signal intensity or as an image map of the apparent diffusion coefficient (ADC). Calculation

of the ADC requires 2 or more acquisitions with different diffusion weightings. A low ADC corresponds to high signal intensity (restricted diffusion), and a high ADC to low signal intensity (as would be seen with T2 shine through). In the setting of acute cerebral ischemia, if the cerebral blood flow is lowered to 15-20 ml/100gm/min, the cell membrane ion pump fails and excess sodium enters the cell, which is followed by a net movement of water from the extracellular to intracellular compartment and cytotoxic edema. Diffusion of the intracellular water molecules is restricted by the cell membranes. The restricted diffusion results in a decreased ADC and increased signal intensity on density-weighted images. Conventional anatomical T2-weighted and FLAIR imaging sequences allow visualization of late tissue damage. Similarly but at lower spatial resolution the b=0 diffusion sequence acquired during DWI is T2 weighted and has the advantage that it is essentially co-registered with the other diffusion images and can be rapidly acquired. Lesion volume changes over time but the initial volume of the stroke on diffusion imaging correlates well with late infarct volume on MR.[83,84] There is a correlation between initial diffusion-weighted volume and NIHSS at later time points[85] (r=0.86), although clinical outcome is dependent on more than just lesion volume.

Dynamic-susceptibility contrast enhanced perfusion-weighted imaging (PWI) requires a bolus injection of gadolinium contrast.[86] Currently this is used to provide information on relative cerebral blood flow (rCBF), cerebral blood volume (rCBV) and mean transit time (rMTT) and with more complex post-processing can yield quantified perfusion measures.[87,88,89] Findings of perfusion-diffusion mismatch (volume of the MTT perfusion deficit larger than the diffusion abnormality early after stroke symptom onset) have led to investigation of the concept of an "ischaemic

penumbra". This is an area of tissue surrounding the core of an infarct that has reduced blood flow but is still potentially viable,[90,91] which may be salvageable if blood flow is rapidly re-established.[92] A number of studies have explored perfusion-diffusion mismatches at various time points to trace the natural history of ischaemic lesions[93,94,95,96,97,98,99]. These studies show that mismatches have some predictive ability for defining final outcome when used in acute stroke[100]. Not all penumbral areas go on to infarct at follow-up and some DWI lesions "grow" beyond the initial perfusion deficit. Currently there are clinical trials looking at response to thrombolysis in relation to mismatch[101,102] and some groups are using mismatch to select patients for thrombolysis.[103] Visual estimation of the three-dimensional (3D) mismatch is difficult and it is not clear whether the human eye can reliably identify patients with mismatch.

3D time-of-flight MR angiography (MRA) allows visualization of the site of vascular occlusions. We have shown that training improves the reliability of MRA interpretation but that it correlates well with conventional angiography.[104] In addition the use of post-contrast MRA better delineates arterial patency over conventional TOF MRA with only modest impact from increased venous and soft tissue enhancement.[105]

1.6. Aims/ Hypothesis:

The hypothesis of this study is that simple CT and MRI baseline characteristics can be reliably acquired in acute ischemic stroke patients and can be used to predict clinical outcome in acute stroke patients, minor stroke patients and TIA patients.

Specific hypotheses include:

1. That the use of ASPECTS to quantify the amount of early ischaemic damage on a NCCT in every day clinical use (real time) is reliable. This has been shown to be of use in the prognosis of stroke patients', however the scale will not be useful until it can be performed in real time.
2. That the ASPECTS score can reliably be scored on CTA-SI and will better predict final infarct volume than ASPECTS based on the NCCT alone.
3. Mismatch between PWI and DWI is being increasingly used to select patients for thrombolysis. We hypothesized that the human eye could not reliably identify mismatch on MRI.
4. That the presence of lesions on diffusion weighted imaging and vessel occlusion on intracranial MRA in minor stroke and TIA patients would predict clinical outcome and recurrent events.
5. That using simple patient baseline clinical and MRI characteristics it is possible to predict recurrent MRI events (clinically symptomatic or asymptomatic).

2. Chapter 2: GENERAL METHODS

This study is a prospective cohort study assessing non-contrast CT and multi-modal MRI in acute stroke and TIA patients. This chapter describes the methods for the overall data collection. Specific projects within the overall study are described in the chapters that follow.

2.1. Inclusion Criteria

Patients presenting to the Foothills Medical Centre, emergency department with:

Persistent focal neurological deficit or transient ischaemic attack consisting of hemiparesis or aphasia lasting >5 minutes

Age > 18

< 12 hours from time last seen normal

Premorbid status modified Rankin 2 or less

Baseline imaging performed within 3 hours of hospital arrival in stroke patients and within 24 hours of hospital arrival in TIA patients.

When tPA is given all imaging modalities will be initiated prior to or early into tPA infusion.

2.2. Exclusion criteria

CT scan evidence of hemorrhage or tumor

Classic migraine features (fortification spectra, zigzag lines, march of sensory symptoms)

Hypoglycemia (serum glucose <2.0 mmol/l)

Serious comorbid illness that would result in the patient being unlikely to survive 3 months or contaminate evaluation scales (eg. NYHA IV CHF, metastatic cancer, severe liver disease) or patient unlikely to be able to meet all follow-up appointments

Seizure is definitely thought to be cause of deficits

Obvious psychogenic cause of deficits

2.3. Informed Consent

A consent form was reviewed with all eligible patients outlining the risk and benefits of the study (appendix 1). Consent was also obtained to collect and store data. If a patient was incapacitated by the stroke and unable to give informed consent, the next of kin or legal guardian was approached to give consent. If a subject later was able to consent the consent process was reviewed with that person to determine whether they wished to continue participating in the study. Patients who underwent intra-arterial (IA) tPA or any concurrent clinical trial were included.

2.4. Baseline Clinical Data Collection

The following demographic information was collected: age, gender; handedness, cerebrovascular risk factors, antithrombotic use, other premorbid disease, time last seen normal, and side of symptoms. See appendix 2. Initial blood pressure recording at triage, serum glucose, International Normalized Ratio (INR) and platelet count on admission was collected. If tPA is given, time of bolus and route(s) of administration were collected. If a patient was enrolled in a therapeutic clinical trial this was recorded.

A baseline National Institutes of Health Stroke Score (NIHSS)[106] (appendix 3) was performed prior to baseline imaging (other than NCCT). The NCCT is part of routine clinical practice and often performed before the stroke team is consulted particularly in the minor stroke and TIA group of patients. The patient or next of kin

was interviewed to determine the premorbid modified Rankin Scale[107,108] (Appendix 4).

2.5. Baseline Imaging and interpretation

2.5.1. Non contrast CT

An investigator blind to MRI information assessed the baseline CT scan. The investigator had knowledge of the patient's affected side only. A noncontrast CT scan was performed on the multi-slice CT scanner. The scans were assessed for the presence of hemorrhage, parenchymal hypoattenuation in the anterior, middle, or posterior cerebral artery territories and the vertebrobasilar artery distribution, focal swelling, hyperdense middle cerebral artery (HMCA) sign, and MCA "dot" sign. The MCA territory was scored using ASPECTS[65,67](appendix 5). CT imaging was optimized using our standard imaging protocol which optimizes detection of early ischaemic changes.[67] Scans were rated by stroke neurologists trained in ASPECTS. (Appendix 6)The CT scan was also assessed for ASPECTS prospectively by the treating physician in real time clinical use.

2.5.2. CT bolus study (CT angiography and CT perfusion)

When clinically indicated (but not mandated in the study) a CT bolus study was performed on the multi-slice CT scanner. The CTA was assessed for evidence of tissue hypodensity and for vascular occlusion or diminished flow.

2.5.3. Multimodal MRI (mMRI)

All patients were screened for contraindications to MRI or to gadolinium contrast agent before they entered the scanner. The MRI was performed on the 3T magnet (Signa; General Electric, Waukesha, WI) in the Seaman Family MR

Research Centre. The sequences acquired were a sagittal T1 localizer, axial DWI, axial FLAIR, axial T2-weighted, pre-gadolinium contrast time of flight MRA, axial PWI and post gadolinium contrast time of flight MRA. This set of sequences and the preparation time took no more than 30 minutes to perform. A power injector was used to administer contrast agent. The baseline multimodal MRI scan was assessed by a neuroradiologist blind to CT information. The investigator had knowledge only of the patient's clinically affected side. A graded assessment of image quality was made taking into account motion and other artifacts. Information was collected on the vasculature, the tissue (new and old lesions, white matter disease etc.) and on the cerebral perfusion (Appendix 7).

2.5.4. Perfusion

Perfusion weighted sequences was used to create relative mean transit time (rMTT) graphs and maps. The rMTT delay between a region of interest positioned over the area corresponding to the largest DWI lesion and the mirror-image area on the unaffected side was recorded. The presence of any rMTT map lesion and its extent in comparison to the extent of the DWI lesion was recorded. This was recorded as showing evidence of mismatch or not. The negative enhancement integral algorithm was used to create a relative cerebral blood volume map. The presence of any oligemia or hyperemia with respect to the unaffected side was noted and the presence of mismatch between the extent of oligemia and the DWI lesion extent was observed.

2.6. Clinical Follow up

All patients were either admitted to a stroke unit or to a high dependency unit if intensive care was required. NIHSS score was recorded at 24 hours while in hospital. NIHSS was also performed at 30 days and 90 days. The 30 day NIHSS and modified QVSFS (Questionnaire for verifying stroke free status, Appendix 8)[109] was performed at the time of follow-up MRI. All patients were assessed at 3 months post event and an NIHSS and modified Rankin score was performed. The physician assessed whether further strokes have occurred, which would impact on the final outcome scores, using a modified QVSFS. The final diagnosis and TOAST classification were recorded. The date of any recurrent stroke (ischaemic or hemorrhagic) or TIA was recorded as well. (Appendix 9)

2.7. Follow up Imaging

MRI was repeated at 1 month (± 2 weeks) post stroke. The MRI protocol consists of identical sequences to those performed at baseline with the exception of the perfusion weighted study. If a MRI was not completed or is contraindicated a NCCT was obtained. The follow-up scan was assessed by an investigator blind to all baseline information. (appendix 10 for MRI and 11 for CT)

2.8. Storage of data

Clinical and radiological data collected was stored in paper and in electronic form. The data base used was constructed using Access and allowed queries of all or part of the database. The database was maintained by me and the accuracy of any information was verified by me.

2.9. Statistical analysis

Data analysis is described for each subsection in the individual chapters. I am indebted to Dr Michael Eliasziw PhD and Dr Michael D. Hill MD for their help with the statistical analysis.

3. Chapter 3: Reliability of ASPECTS performed in real time

As described in the introduction ASPECTS is a 10 point scale rating the early ischaemic changes seen in acute stroke in the middle cerebral artery territory on CT. Previous studies of ASPECTS have been done with consensus assessment[56] or not prospectively[65]. In this project we describe the reliability of ASPECTS rated prospectively by the treating physician as compared to the ASPECTS performed at a later date by an expert rater.

3.1. Methods

Prospectively 214 patients were recruited into this study. Inclusion criteria were stroke or transient ischaemic attack (consisting of hemiparesis or aphasia lasting more than five minutes) that were scanned within 12 hours of last seen well, were older than 18 years of age and were functionally independent on the modified Rankin scale (score 2 or less). All patients presenting with the above characteristics were included, not just middle cerebral artery syndromes. Patient demographics were recorded at the time of admission to the emergency department. The protocol was approved by the local institutional ethics review board.

3.1.1. Imaging

Standard non-contrast CT was performed with a 4th generation multi-slice CT scanner (GE Medical Systems) in the emergency room. The non-contrast CT scanning technique was as follows: 120kV, 170mA, 2-second scan time, and 5-mm slice thickness. Coverage was from skull base to vertex with contiguous axial slices parallel to the inferior orbitomeatal line. A window width of 75-80 HU and window level of 30-40 HU were used to maximize tissue contrast. Physicians were able to

alter the window width and leveling as appropriate to maximize the appearance of ischaemic changes[110].

3.1.2. Image Analysis

The ASPECTS was recorded prospectively by the treating physician at the time of CT scan. The treating physician (stroke fellow or stroke neurologist experienced in rating ASPECTS) scored the ASPECTS without knowledge of any other imaging modalities, but with knowledge of clinical symptoms. At a later point one of four expert readers (different individual than the treating physician; including one neuroradiologist, two stroke neurologists and one stroke fellow) rated the baseline CT scan using ASPECTS. The expert reader was blind to all clinical information and previous ASPECTS. The expert reader however had knowledge of the symptom side. Each scan was read by the treating physician and later by one expert reader.

3.1.3. Statistics

Descriptive statistics were used to evaluate the study population. Inter-rater reliability between experts was not measured, but the reliability between experts has been previously shown to be equivalent.[66] Agreement between the real-time and expert ASPECTS rating was assessed using weighted kappa (κw) scores. The weighting was designed to heavily penalize any difference greater than 1 ASPECTS point. κw values were interpreted as slight agreement 0.00-0.20, fair agreement 0.21-0.40, moderate agreement 0.41-0.60, substantial agreement 0.61-0.80 or almost perfect agreement 0.81-1.00.[111]

The distribution of ASPECTS scores (real time and expert) was skewed. The differences between the real-time and expert ASPECTS scores were normally

distributed. The unit of analysis was the difference between the real time and expert ASPECTS. Analysis of variance was used to assess the difference between categories of real time ASPECTS values and the difference between the real time and expert ASPECTS. Hypothesis testing between groups was adjusted using the Bonferroni method. Linear regression was used to plot this relationship.

3.2. Results

There were 214 patients included in this study between May 2002 and July 2003; 88 (41%) were female. The median baseline NIHSS was 5 (range 0-32). Median age was 72.5 (27-91). Fifty-four patients had a transient ischaemic attack by the current definition[39] (NIHSS = 0 at 24 hours). Median time from symptom onset to CT scan was 152 minutes (range 22-769 minutes).

Inter-observer agreement between real time and expert ASPECTS was substantial; κw=0.69 (95%CI 0.59-0.79). The mean difference was 0 (SD 1.1). There was no difference in the reliability if transient ischaemic attack patients were excluded (κw=0.66, n=160) or if only patients scanned at under 6 hours are considered (κw=0.68, n=183) or if only stroke patients scanned at under 6 hours are considered (κw=0.65, n=140).

Trichotomizing the ASPECTS scale into <3 (unfavourable); 3-7 (neutral) and 8-10 (favourable) had no impact on the mean differences between real time and expert ASPECTS, except when the real time ASPECTS was <3. In this situation the expert reader was likely to call the scan approximately two ASPECTS points greater than the treating physician (p=0.007 for 3-7, and p<0.001 for 8-10). There was a trend towards the treating physician under calling the ischaemic change in the 8-10

group i.e. the treating physician gives a clinically more favourable score than the expert. However this did not reach statistical significance (p=0.064). This relationship was not affected by age, blood glucose or the baseline NIHSS score.

Figure 1 gives a graphic representation of the correlation between the real time ASPECTS and the difference between the real time ASPECTS and the expert ASPECTS. The slope of the line suggests that at lower real time ASPECTS ratings, there is a trend for the treating physician to over-interpret the presence of ischaemic change. (Figure 2)

3.3. Conclusions

The reliability of rating ischaemic change on the acute stroke CT in routine clinical practice compared to expert rating has not been previously evaluated. We have found that ASPECTS is reliable between real time and expert ratings. This is important because the true significance of a clinical scale is its ability to be used in routine clinical practice. However, it must be emphasized that this clinical scale is only useful for the middle cerebral artery territory strokes and not the PCA or ACA.

At higher ASPECTS (>7) scores (favorable scan appearance) the real-time observer tends to under-call ischaemic change. The effect size is quite small and is likely to be clinically insignificant. There are many possible reasons for this, but if this effect is real it is likely due to the physicians wish to treat the patient with thrombolysis.

At lower ASPECTS (<3) scores (unfavorable scan appearance) the real-time observer tends to over-call the ischaemic change by nearly two points. The reasons for this probably reflect a combination of factors including the visual perception

system's tendency to overestimate boundaries.[112] Human factors such as a desire not to administer thrombolysis may also spur the real-time observer to naturally err toward lower scores. This effect is possibly an overestimation of the effect due to the fact there are only 6 patients in this group There was no relationship between NIHSS and the differences seen between the real time and expert ASPECTS. This suggests that the real time physician does not overcall ischaemic change due to bias introduced by knowledge of stroke severity. At the high end of the scale, the physician may be keen to offer thrombolysis and under-interpret the ischaemic change. A final reason for disparity in scoring between the real time and expert rating is that the treating physician often does not have ideal conditions for the rating of brain CT scan.

A weighted Kappa was used for the statistics since artificially dichotomizing the results into >7 and <7 would overly penalize a scan that an expert called a 7 and the treating physician called a 6. A score of ± 1 point on the ASPECTS scale has been to shown to the expected margin of error[66], is felt not to be clinically significant and would not deter thrombolytic treatment for any given patient. Hence the Kappa score was weighted to penalize any difference more than ± 1 point. This is a potential limitation of this study, however to regard scores of 8 or 9 as different may artificially disadvantage a simple scale.

Our population included patients with transient ischaemic attack and patients who were imaged between 6 and 12 hours after symptom onset. However removing these patients from the analysis made no difference to agreement.

The results in our study are limited to stroke neurologists and neuroradiologists. We did not assess the ability of emergency physicians or trainees

to rate ASPECTS. This is an important limitation and future work is needed in this area.

In conclusion we have found that ASPECTS performed in real time is a reliable method of quantifying the early ischaemic changes of the middle cerebral artery in acute stroke.

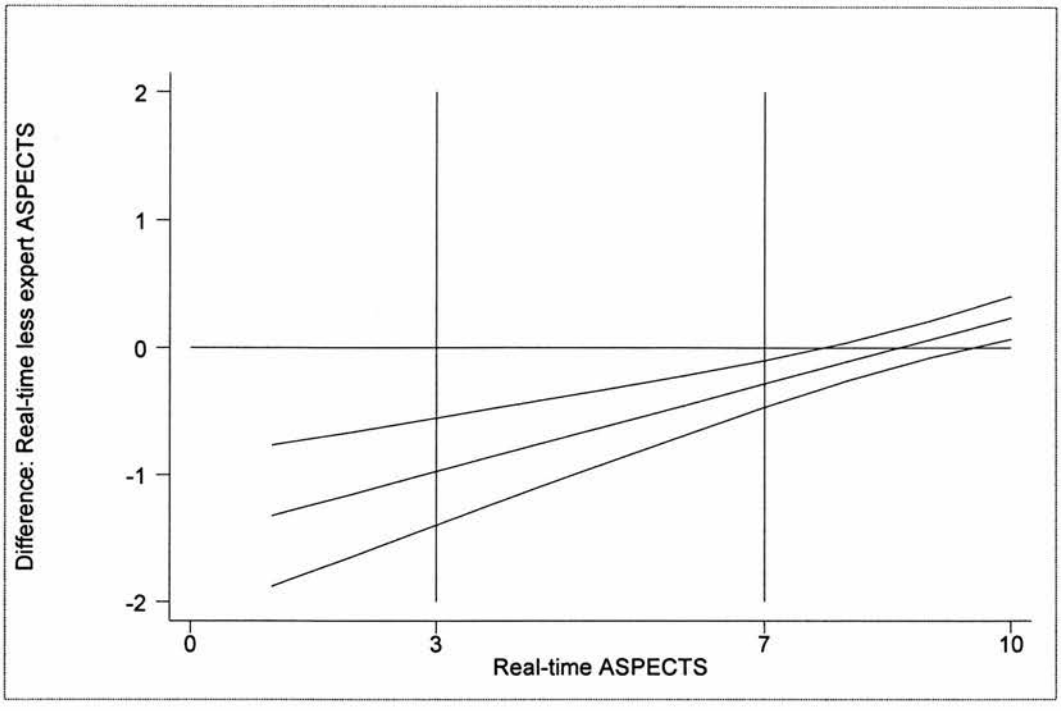


Figure 1: Graphic representation of the real time ASPECTS compared to the real time ASPECTS- Expert ASPECTS. The slope of the line suggests that at lower real time ASPECTS ratings, the treating physician is likely to over-call the presence of ischaemic change. Outside lines show 95% confidence intervals

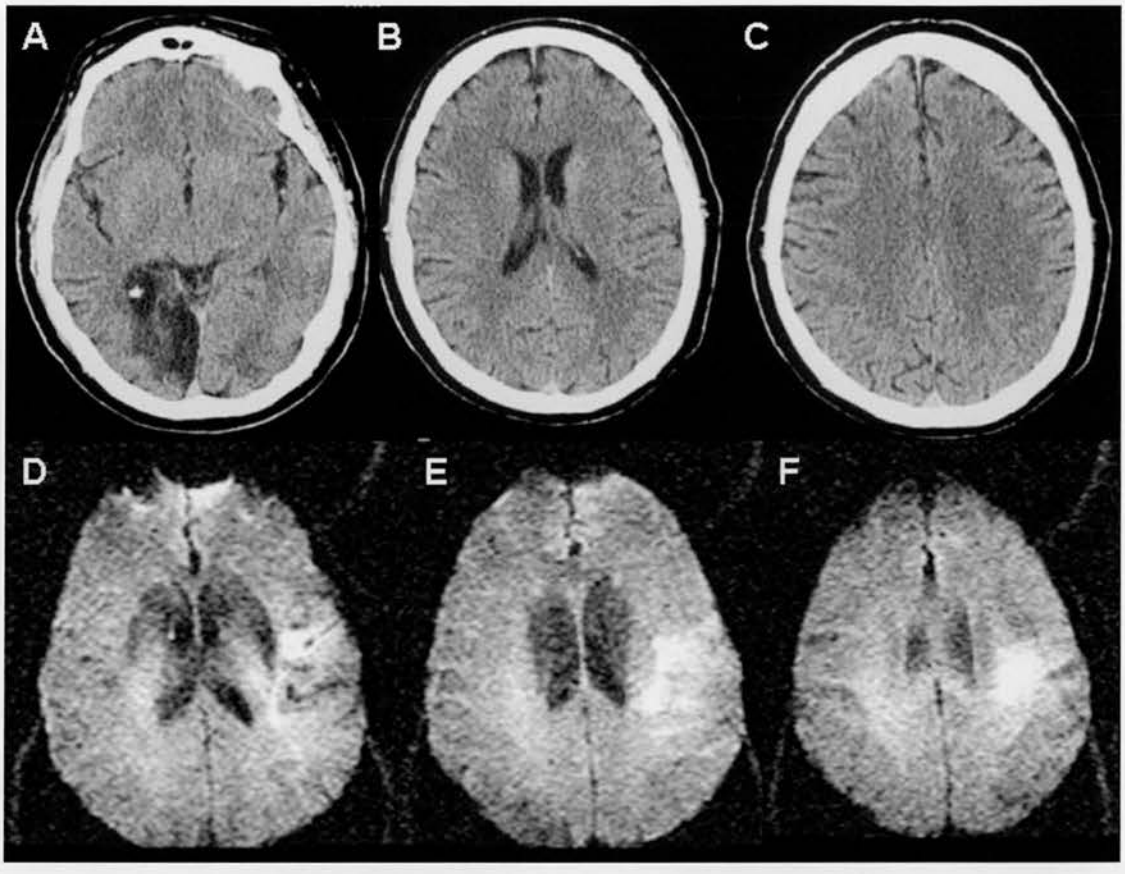


Figure 2: Overcalling in Real time. A, B and C show the representative cuts from a CT scan performed at 3 hours and 8 minutes after symptom onset on an acute stroke patient with right hemiparesis and aphasia (NIHSS 16). The treating physician rated the scan as having an ASPECTS of 4 with regions: Insula, M2, M3, M4, M5 and M6 rated as abnormal. Later expert review of the scan rated the scan as having an ASPECTS of 7 with regions: Insula, M2, and M3 rated as abnormal (MCA dot sign seen on cut A). C, D and E show the diffusion weighted MR performed 4 hours and 40 minutes after symptom onset. An evolving infarct is seen in ASPECTS regions; Insula, M2, M3, and M5 (total score 6).

4. Chapter 4: ASPECTS on CTA Source Images versus unenhanced CT: Added value in predicting final infarct extent and clinical outcome.

We sought to assess whether the final infarct ASPECTS and clinical outcome were associated with the acute CTA-SI ASPECTS.

4.1. Subjects and Methods

4.1.1. Patients

We assessed the clinical and imaging information of consecutive patients with acute ischaemic stroke from two institutions, who had NCCT and CTA (18 patients from Departments of Radiology and Neurology, Massachussetts General Hospital, Harvard Medical School, Boston and the other 21 from Foothills Hospital in Calgary). Stroke onset was defined as the time the patient was last seen well. Exclusion criteria were CT scan evidence of hemorrhage or tumor, hypoglycemia (serum glucose <2.0 mmol/l), serious comorbid illness that would result in the patient being unlikely to survive 3 months or contaminate evaluation scales or a patient who did not complete any follow up imaging due to severe neurological deterioration, age<18, premorbid status modified Rankin >2 or symptoms suggestive of a posterior circulation event. Exclusion criteria specific for CTA were, a known history of contrast medium allergy or any degree of renal failure. Patient demographics and clinical characteristics were recorded at the time of admission to the emergency department. All patients received intra-venous or intra-arterial thrombolysis if appropriate as indicated by their clinical findings. Informed consent was obtained from the patient or their next of kin and this project was approved by the local institutional ethics committees of both institutions.

4.1.2. Imaging

Standard NCCT was performed with a multi-slice CT scanner (GE Medical Systems) in both institutions using 120kV, 170mA, 2-second scan time, and 5-mm

slice thickness. Coverage was from skull base to vertex with contiguous axial slices parallel to the inferior orbitomeatal line.

NCCT scanning was followed immediately on the same scanner by CTA imaging with a helical scan technique. Previous work has shown that this adds around 10 minutes to the scanning time.[77] Acquisitions were obtained following a single bolus intravenous contrast injection of 90 to120ml of nonionic contrast into an ante-cubital vein at 3 to 4 ml/sec with a 20 to 25 sec delay from the start of the contrast injection to the onset of imaging. The image sequence covered the foramen magnum to centrum semiovale or vertex with a scan field of view (25.0 cm; 140 kV, 170 mA; Table speed 3.75mm/sec; 2.5mm slice thickness with 2.5mm interval; 1.0 sec per rotation). Source images (CTA-SI) were reconstructed to 1.25mm thickness at 0.625 mm intervals.

Follow up imaging was performed on all patients. T2-weighted MR imaging was substituted among patients for whom follow-up NCCT was unavailable. All follow up imaging was performed at a minimum of 24 hours after symptom onset. Clinical outcome was assessed by a stroke neurologist using the modified Rankin Scale during an in-clinic visit. If a patient was unable to return to clinic either the modified Rankin was completed by telephone or a physician attended the nursing home to complete the clinical scales. Favorable patient outcome at 90 days was defined as a modified Rankin score of 0 or 1.

4.1.3. Image analysis

The assignment of an ASPECTS to each patient's image was performed independently by a neuroradiologist and a stroke neurologist. Both readers were

experienced in the interpretation of CT scans in acute stroke. Two other individuals, a neuroradiologist and a stroke neurologist, interpreted a subset of images for calculation of inter-rater agreement. Raters were blinded to all clinical information except for symptom side. The scoring of NCCT, CTA-SI images and follow up imaging (NCCT or MRI-FLAIR) were in a random order. Baseline and follow-up imaging interpretation was spaced over several weeks.

All images were reviewed digitally at a workstation with a large high-resolution monitor. Care was taken to use optimal width and level settings during CT image review to maximize the contrast produced by the small attenuation difference between normal and hypodense brain parenchyma[110]. NCCT images were evaluated for evidence of focal parenchymal low attenuation, loss of grey-white differentiation and sulcal effacement using ASPECTS as previously described[67]. On the CTA-SI, regions of relatively diminished contrast enhancement were scored as abnormal (figure 3). The CTA-SI were viewed at the window and level that allowed the maximum contrast between normal and ischaemic tissue[110]. The CTA-SI and circle of Willis maximum intensity projection reconstructions of the CT angiogram were evaluated for the presence of occlusion. ASPECTS on MRI was assigned in a similar manner to NCCT, as previously described.[113]

4.1.4. Statistical Analyses

The unit of analysis was the mean of the two readers' ASPECTS. A two-factor repeated measures analysis of variance was used to compare the mean baseline ASPECTS between NCCT and CTA-SI. In the analysis of variance, the between-subject factor was the follow-up ASPECTS, categorized as 0 to 3, 4 to 7, and 8 to 10. The within-subject factor was the baseline ASPECTS, because the NCCT and CTA-

SI scores were obtained from the same patient's CT scan. Rate ratios (RR) were used to quantify the relationship between the dichotomized baseline ASPECTS (categorized as 0-7 versus 8-10) and favorable patient outcome. The chosen cut point has been previously used as a cut point above which benefit is seen in using intra-arterial thrombolytic therapy for acute ischaemic stroke patients.[56] Inter-rater agreement in assigning ASPECTS was estimated using an intra-class correlation coefficient computed from a one-way analysis of variance.

4.2. Results

A total of 39 patients were recruited between May 2002 and May 2003. There were no adverse events related to the use of the contrast medium. Demographic results are described in this section as median and the interquartile range is shown. The median age of the patients was 74 (62 to 81) years and 54% were female. The median baseline NIHSS was 16 (9 to 22) and 90% of the patients were treated with tPA. 4 patients were treated with iv/ia therapy, 13 were treated with iv alone and 18 were treated with ia tPA alone. The median time between symptom onset and imaging was 1.9 (1.2 to 2.5) hours, with 41% of the scans performed within 90 minutes of symptoms. Proximal occlusion (ICA or MCA) on CT was identified in 62% of the patients, M2 occlusion in 18%, and no large vessel occlusion in 20%. The follow-up scan was performed at a median time of 10 (4 to 34) days. T2-weighted MR imaging was substituted for follow-up NCCT in 14 (36%) patients.

The overall mean baseline ASPECTS differed by 1.1 (p-value < 0.001). Figure 4 summarizes the mean differences at each follow-up ASPECTS category. There was a significantly larger difference of 1.4 between the mean baseline NCCT

and CTA-SI ASPECTS in patients who had more ischaemic changes (follow-up ASPECTS = 0 to 3) than a difference of 0.6 in patients who had near-to-normal CT scans (follow-up ASPECTS = 8 to 10). There were no cases of CTA-SI overestimating the final infarct size. In 7 of the cases that ultimately had a stroke (follow-up ASPECTS <10) one reader interpreted the NCCT as normal (ASPECTS 10), but interpreted the CTA-SI as showing at least some ischaemic change (ASPECTS<10). There was no evidence of reversibility of CTA-SI seen in this study. Figure 5 shows a scatter plot of mean ASPECTS scores for CTA-SI and NCCT as compared to final ASPECTS scores on follow-up imaging.

The rate of favorable outcome for NCCT ASPECTS of 8-10 was 51.8% versus 25.0% for 0-7 (RR = 2.1, 95% CI: 0.7 to 5.9, p-value=0.12). For CTA-SI ASPECTS of 8-10, the rate of favorable outcome was 58.8% versus 31.8% for 0-7 (RR = 1.8, 95% CI: 0.9 to 3.8, p-value = 0.09). The inter-rater agreement for baseline ASPECTS using NCCT was 0.71 versus 0.73 for CTA-SI.

4.3. Discussion

Acute ischaemic stroke requires urgent assessment of the clinical and radiological features of the brain insult. The ability to identify an acute infarct on CT is helpful in confirming the diagnosis of acute stroke[63]. A completely normal non-contrast CT scan, seems ideal in terms of potential benefit (since no damage is currently seen) from any possible therapies, but may introduce diagnostic uncertainty for the stroke neurologist. Normal scans early into acute stroke are reasonably common. The ECASS II experienced reviewers did not detect early ischaemic changes in about 1/3 of infarcts that later appeared on follow-up CT[114] and the

NINDS investigators reported that only 31% of patients in the NINDS tPA trial had evidence of early ischaemic changes.[115] Our results suggest that CTA-SI ASPECTS has a greater sensitivity to ischaemic changes and more accurately identifies the volume of tissue that will ultimately infarct compared to NCCT alone. The cases where one rater scored the scan as 10 show the potential advantage of using CTA-SI. In 7 of these cases the ischaemia would have been totally missed by one of the expert raters. It is in this setting (ASPECTS = 10 of the NCCT) where CTA-SI is most likely to be helpful. However one could also argue that this would not make a difference since most physicians would not withhold thrombolytic therapy on the basis of a normal scan. In situations where the clinical diagnosis is unclear however the CTA-SI may be potentially very helpful.

CTA is one method of quickly and accurately identifying vessel occlusion and ischaemia. Using a follow up ASPECTS as the final infarct size, CTA-SI gives a more accurate estimate of tissue that is at risk of infarcting than does a NCCT alone. The value of a combined CTA, CTA-SI over NCCT in predicting clinical outcome has also been demonstrated using a scale that differs from ASPECTS.[116]

It is important to recognize that hypoattentuation on NCCT and CTA-SI hypoattenuation probably imply different pathophysiologic abnormalities. These may not always represent core of infarction. A CTA-SI region showing a lack of enhancement provides an estimate of CBV[76,77] while NCCT measures shifts in brain tissue water content. It is the net uptake of water in brain regions with hypoperfusion less than 12 ml/100 g x min[117,118] that causes hypoattenuation. Large shifts of water are needed for the human eye to visualize hypoattenuation. Animal studies have shown that a 1% increase in brain water content results in an x-ray attenuation

decrease of 2-3 HU[119]. Optimal window width and leveling[110] can help to identify reliably such changes in water content. Recent work confirms that the volume of abnormality on CTA-SI at baseline is a very close match to the volume of final infarct on follow up scanning if there is prompt recanalization[77]. Further work is needed on this subject.

Both NCCT and CTA-SI showed a trend towards a better clinical outcome for baseline ASPECTS of 8-10. This is consistent with observations from the PROACT-2 trial where an ASPECTS of 8-10 was found to differentially predict response to thrombolytic treatment.[56] Larger numbers of patients will be needed to assess and confirm the relationship of ASPECTS on CTA-SI with clinical outcome.

The possibility of CT fogging effect is a relative limitation of our study. The timing and degree of fogging is variable, and has mostly been studied in small series, on older generation CT scanners.[120,121] More recent papers suggest that fogging can start as early as 5-10 days post ictus, but that it may also occur months after stroke onset, coincident with the time period of post stroke hyperemia[122] (a potential mechanism of fogging). The timing and degree of fogging likely varies with factors such as infarct size, as well as the severity of the initial deficit.[123] Importantly for our results, previous work suggests that fogging of large infarcts is typically not complete.

Another potential limitation of this study is the fact that the CTA was always performed after the NCCT. Previous studies using CTA in this protocol however has shown that the CTA is only delayed by around 10 minutes as compared to the NCCT. This is one potential reason for the increased ischaemia seen on the CTA-SI.

The reliability of assessing ASPECTS on the CTA-SI was very good and similar to that on non-contrast CT. Larger studies are needed very early from stroke onset to compare both techniques. NCCT changes are particularly difficult to appreciate in such patients and may be greatly aided by CTA-SI information. In centres not used to examining NCCT for early ischaemic changes this technique may aid in the identification of ischaemia.

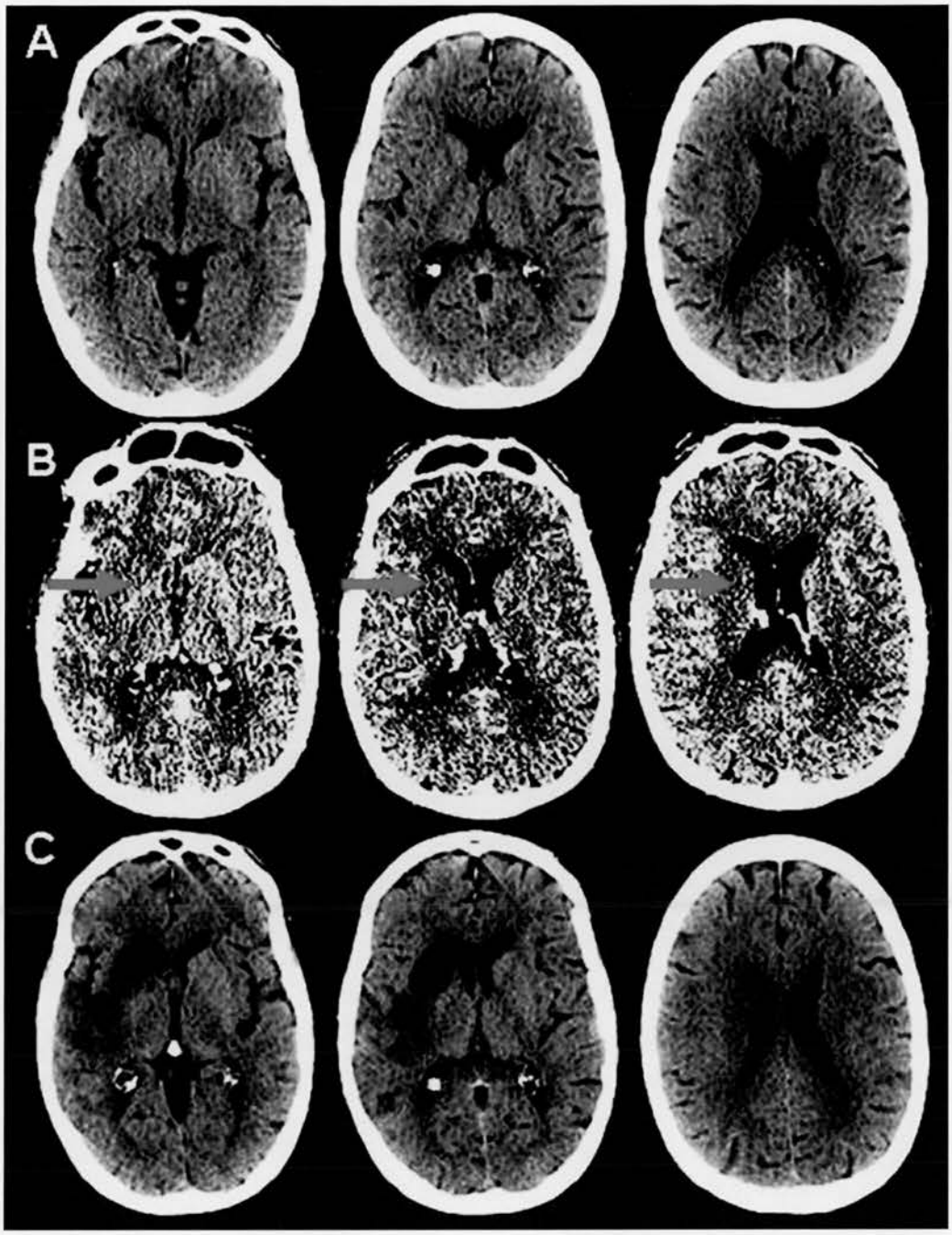


Figure 3: 75 year old man with left hemiplegia and hemineglect syndrome caused by a right MCA occlusion. Unenhanced CT scanning was performed 62 minutes after symptom onset; NIHSS was 15 at baseline. A. Possible subtle right lentiform / subinsular ischaemic hypodensity; this scan received an ASPECTS rating of 10 from one of the experts, and 9 from the other. B.

Corresponding CTA-SI images, obtained immediately following the NCCT, showed unequivocal hypocontrastation involving the caudate nucleus, lentiform nucleus, M2 territory, and insula. Red arrows point out these areas. This scan received an ASPECTS rating of 6 from one of the experts, and 2 from the other. C. Follow-up CT reveals progression to infarction in the territory of the CTA-SI lesions, despite successful vessel recanalization following IV and IA rt-PA. The raters scored the follow up scan as having ASPECTS of 6 and 5 respectively.

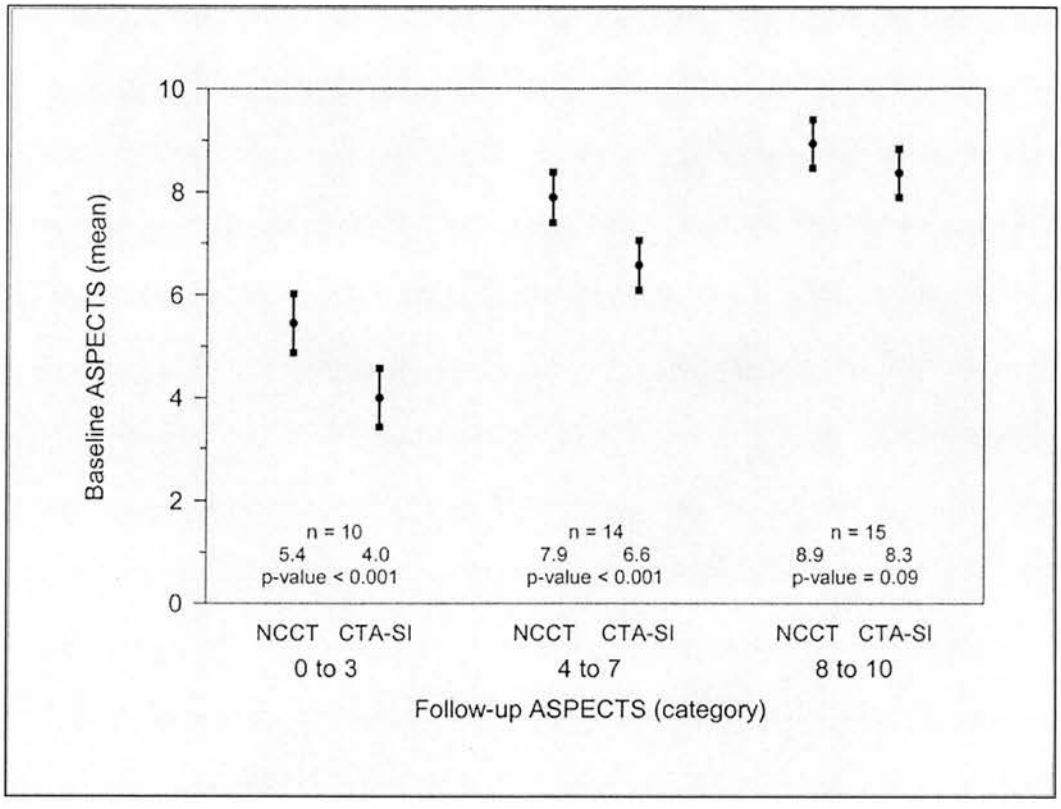


Figure 4: A comparison of mean ASPECTS score at baseline between non-contrast CT (NCCT) and CTA-source images (CTA-SI) according to three categories of ASPECTS scores at follow-up. The 95% confidence intervals about the mean score (vertical lines) and the p-values (along the horizontal axis) were computed from a two-factor repeated measures analysis of variance. The p-values correspond to comparing the mean scores (reported above the p-values) between NCCT and CTA-SI for each category of follow-up ASPECTS score. In general, the baseline ASPECTS score for CTA-SI was lower than for NCCT and was closer to the midpoint of the category for the follow-up ASPECTS score.

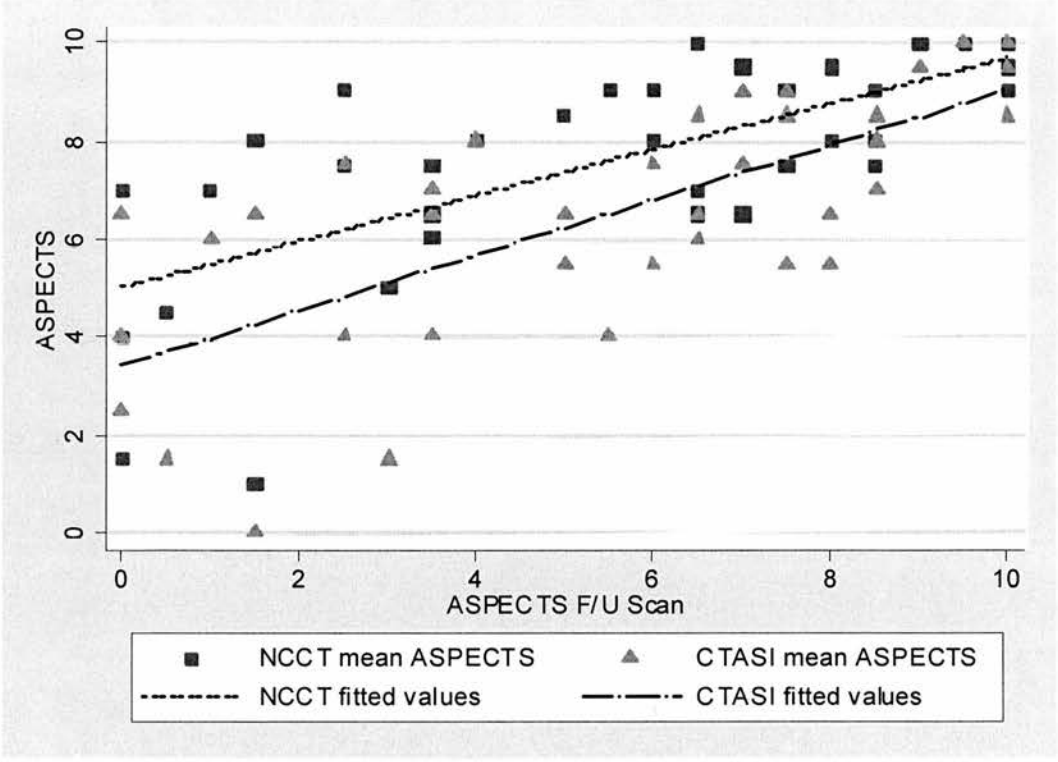


Figure 5: Scatter plot of mean ASPECTS scores for CTA-SI and NCCT compared to final ASPECTS scores on follow-up imaging. The estimated lines are derived from simple linear regression equations and imply that there is a consistent difference between NCCT ASPECTS and CTA-SI ASPECTS regardless of final infarct volume.

5. Chapter 5: Reliability of Assessing Percentage Diffusion-Perfusion Mismatch

In acute stroke when the acute PWI lesion volume is larger than the DWI lesion volume (referred to as mismatch) often the stroke evolves and grows.[124,125,126] Tissue with hemodynamic change but without DWI ischaemic lesions may be salvageable. Thus, mismatch has come to be used in patient selection for thrombolysis.[103] Visual estimation of the three-dimensional (3D) mismatch is difficult. The aim of the present study was to examine the inter- and intra-rater reliability of visually estimating the percentage mismatch. The study parameters were chosen to mimic a clinical real-time assessment of mismatch that would be used to inform clinical decision making regarding thrombolysis.

5.1. Methods

5.1.1. Patients

The present study was part of an institutionally approved protocol of emergency MR imaging of acute stroke patients performed from October 1999 to February 2002. Thirteen patients were selected retrospectively from the acute stroke MR database. An investigator who was not a rater selected study subjects randomly from the database. All patients were scanned within seven hours of symptom onset, showed evidence of diffusion- (with restricted apparent diffusion coefficient (ADC)) or perfusion-weighted MRI changes, and had optimal scan quality. Patients were chosen to reflect a variety of diffusion and, perfusion lesion sizes, location of infarct and clinical characteristics. The scans included examples of large, medium and small mismatch (PWI > DWI), as well as examples of matched (PWI=DWI) and reverse mismatch (PWI<DWI).

5.1.2. Imaging Protocol

MR images of the brain were obtained using a 3-Tesla scanner (Signa; GE Medical Systems, Waukesha, WI) equipped with high performance gradients (40 mT/m, 184-μs rise time). All imaging was performed using a standard quadrature head coil. The acute stroke imaging protocol included standard anatomic imaging (T2-weighted, FLAIR and magnetic resonance angiography), DWI and PWI. Only the latter two imaging sequences were evaluated in this study. DWI was performed with a single-shot spin-echo echo-planar imaging technique with a diffusion sensitivity of b=1000 s/mm^2, 7000 ms/96 ms (TR/TE), 19 5-mm slices with 2-mm gap, 32 x 19-cm field-of-view (FOV) and a 192 x 192 acquisition matrix reconstructed to a 256 x 256 matrix. PWI used a single-shot gradient-echo echo-planar sequence with 2200 ms/25 ms. Ten 6-mm sections with a 3-mm gap, 32 x 19-cm FOV, and a 192 x 192 acquisition matrix were reconstructed to a 256 x 256 matrix. Five hundred and ten images were collected over 112 s during the intravenous administration of a 20-mL bolus of gadopentetate dimeglumine (Magnevist; Berlex, Wayne, NJ) injected at 5 mL/s. PWI acquisitions on our scanner were limited to collection of a maximum of 512 images. In this study, we chose to collect 51 time-points over 112 s (which necessitated a TR of 2200 ms) and to collect 10 slices at each time point. This long TR was chosen due to the fact that in acute stroke the blood flow is often slow and we need to acquire perfusion maps over the 90 to 120 s range. In order to increase the PWI coverage, the slice thickness and gap were increased compared to the DWI acquisition.

5.1.3. Image analysis

The MR scans were independently assessed twice by six raters (two neuroradiologists, two stroke neurologists and two stroke fellows), blinded to all clinical information. All raters were experienced in assessing the acute changes of stroke on MR imaging. The DWI images were examined for evidence of restricted diffusion on a clinical workstation (Advantage Windows, General Electric Medical Systems). Mean transit time maps (rMTT) were created using manufacturer-supplied software (Functool 2000, General Electric Medical Systems). Each rater was trained and used the same method. A PWI abnormality was considered present if there was any visible abnormality on the rMTT map when viewed on a grey scale. The DWI and PWI images were viewed on the MR workstation simultaneously. Windowing was adjusted by the rater, with no fixed levels designated. If DWI>PWI then the scan was rated as having reverse mismatch. If PWI=DWI then a matched deficit was considered present. If there was no evidence of a DWI lesion, but there was a PWI lesion, then mismatch = 100%. If PWI>DWI then the percentage mismatch between DWI and the rMTT map was estimated [((rMTT volume-DWI volume)/rMTT volume)*100%] to the nearest 10%. This lead to an estimate of the three dimensional mismatch in lesion volumes. The raters repeated the above procedures after a period of at least two weeks, to determine intra-rater reliability.

Four raters manually drew lesion outlines around the DWI and rMTT lesion areas on all images twice, separated by a period of at least one week between each rating. Displayed image contrast (window and level settings) was allowed to be varied to optimize visualization of the lesions. Lesion volumes were calculated for each image and the percentage mismatch calculated where volume = [area x slice number x (slice thickness + interslice gap)].

Estimates of inter-rater and intra-rater reliability and standard error of measurement (SEM) were calculated simultaneously from a two-way random effects analysis of variance.[127] One-sided, lower-limit 95% confidence intervals (CI) were calculated about the estimates. Further analysis of reliability using dichotomized cut off points at 10% and 20% mismatch was conducted. Suggested benchmarks for reliability are as follows: Slight 0.00-0.20, Fair 0.21-0.40, Moderate 0.41-0.60, Substantial 0.61-0.80, Almost Perfect 0.81-1.00[111].

5.2. Results

The sample of patients included six women and seven men. The median age was 65 years (range 45-82 years), median time from symptom onset to scan was 152 minutes (range 72-420 minutes), and the median NIHSS was 5 (range 0-18). An example of a MR scan used in the present study is shown in Figure 6.

For visual assessment representing the state-of-the-art for real-time clinical decision making, the inter-rater reliability among six raters was 0.68 (95% CI: 0.52 to 1.0; SEM=21.6%). The intra-rater reliability was 0.80 (95% CI: 0.47 to 1.0; SEM=16.9%). Using a dichotomised cut-off point of >10% versus ≤10% mismatch, the inter-rater reliability was 0.71 and intra-rater reliability of 0.78. A dichotomized cut-off point of >20% versus ≤ 20% mismatch had lower reliability (inter-rater=0.60, intra-rater=0.72). For PWI-DWI mismatch derived from volume calculations based upon lesion tracing, the inter-rater reliability among four raters was 0.66 (95% CI: 0.45 to 1.0; SEM=26.2%). The intra-rater reliability was 0.94 (95% CI: 0.81 to 1.0; SEM=10.9%).

5.3. Discussion

Results from the present study suggest that quantifying mismatch by the human eye is reproducible, but not reliable among observers. The margin of error between raters was large. For example if one rater was to estimate the percentage mismatch as 10% and another were to estimate it at 40%, then the difference of 30% would still be within the error of the measurement (+/- 21.6%).

The prognostic significance of mismatch where the PWI lesion is defined by the rMTT remains unclear, but this method has made its way into clinical decision making and trial design. For example the Desmoteplase in Acute Stroke (DIAS) trial[102], tests the hypothesis that patients with 20% or greater DWI-PWI mismatch will benefit from use of intravenous desmoteplase in a 3- to 9-hour time window. We conclude from the results of the present study that real-time determination of percentage mismatch may lead to inaccurate clinical characterization for the individual patient. Additionally the failure to account for this error may lead to underpowered clinical trials. However, the level of intra-rater reliability may be sufficient for central review of images by a single individual.

This study was performed at 3.0 T. Imaging at this field strength had a number of advantages and disadvantages compared to 1.5 T. Within the context of this study, 3.0 T imaging would intrinsically have had a higher signal to noise ratio, which was used to acquire higher than typical resolution DWI and PWI data. DWI contrast is independent of field strength, whereas PWI contrast in T2*-weighted imaging increases with field strength. In this study the echo time at 3 T (25 ms) was reduced to compensate for the additional T2*-weighting.

Advances leading to rapid creation of quantified perfusion maps and computer-assisted volume measurements[128] may obviate the need for visual estimates of mismatch in the future. In the interim we would caution the use of visual inspection of mismatch as the deciding factor in treatment or trial enrolment.

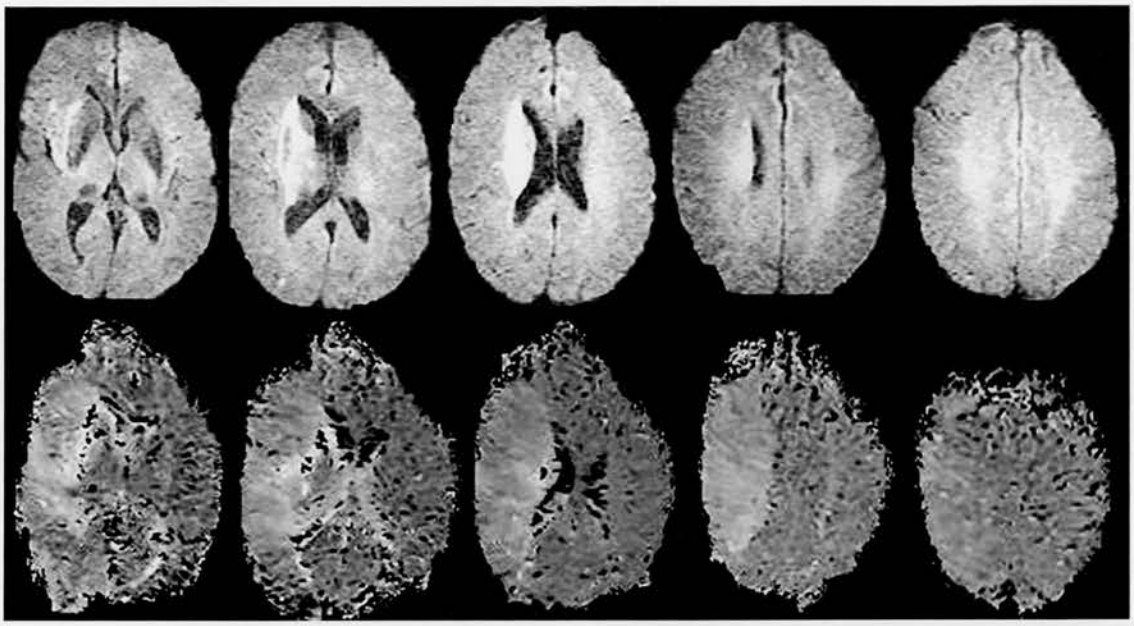


Figure 6: Top row shows DWI changes in the right MCA territory. Second row show the rMTT map for this case, with PWI>DWI lesion (mismatch). This case was rated by the six experienced observers as having a mismatch ranging from 30 % to 100 %. The error range of the measurement across all cases is ± 21.6%.

6. Chapter 6: Presence of DWI lesion on acute MRI in minor stroke and TIA patients predicts recurrent stroke and clinical outcome.

Brain imaging may offer the opportunity to better risk stratify those presenting to the emergency room with a non-disabling ischaemic cerebrovascular event. We hypothesized that among patients presenting with a TIA or minor stroke, the presence of a DWI lesion would be predictive of both the future occurrence of stroke and disability at 3 months. Secondary aims of this study were to determine whether either the classical definitions or new proposed definitions of stroke or TIA were predictive of future stroke or disability[33,39].

6.1. METHODS

6.1.1. Patients

We prospectively enrolled consecutive patients presenting to a single academic institution with symptoms of minor stroke or TIA, consisting of hemiparesis or aphasia lasting more than five minutes who were examined by a stroke neurologist within 12 hours of last seen well. Additional inclusion criteria to be met were: NIHSS ≤ 3, older than 18 years of age, and functionally independent on the modified Rankin scale (≤ 2) at baseline. The research protocol was approved by our institutional ethics committee and all participants provided written informed consent. Patient demographics and clinical history were recorded at the time of admission to the emergency department. All patients were examined by a stroke neurologist. TIA was defined according to the World Health Organization criteria[129] as rapidly developed clinical signs of focal or global disturbance lasting fewer than 24 hours, with no apparent nonvascular cause. At 24 hours ± 8 hours, post-symptoms, a stroke neurologist confirmed the diagnosis of TIA if all symptoms had

resolved. The time to symptom resolution was recorded. If the patient's symptoms had not resolved by the time of going to sleep, but had resolved the next morning, the time to resolution was recorded as the time of awakening.

6.1.2. Imaging

MR imaging was performed as soon as possible after arrival in the emergency department and within 24 hours of symptom onset. Images were obtained using a 3-Tesla scanner (Signa; GE Medical Systems, Waukesha, WI) equipped with high performance gradients (40mT/m, 184-μs rise time), using a standard quadrature head coil. Sequences included sagittal T1, axial T2, axial FLAIR, DWI (B=1000), and 3D time-of-flight MR angiography (MRA) of the intracranial circulation.[130] Imaging was assessed by a neuroradiologist blind to all clinical information other than symptom side and any subsequent imaging information if applicable. The four MR sequences DWI, ADC, FLAIR and T2 were examined for presence of a new acute stroke lesion (Figure 7). The MRA was assessed using source images and maximum intensity projection reformats for evidence of vessel occlusion.

6.1.3. Patient outcomes

Patients had a neurological assessment at 24 hours, 1 month and at 3 months after their presenting event to the emergency department. The National Institutes of Health Stroke Scale (NIHSS)[106], modified Rankin scale[131,132] and the Questionnaire to validate stroke-free status (QVSFS)[109] were completed by the neurologist at 1 and 3 months. Occurrence of stroke during follow-up was defined as a functional deterioration in neurological status of vascular origin or a new sudden focal

neurological deficit of vascular origin lasting more than 24 hours. If a patient had a stroke or TIA during follow-up, their brain imaging and clinical records were reviewed by a stroke neurologist to confirm the diagnosis. At 3 months, after reviewing all clinical and imaging information, the final diagnosis of the presenting event was made and the potential mechanism assigned using the TOAST[133] classification.

6.1.4. Statistical Analysis

The primary outcome was new stroke occurring within 90 days of the presenting event. Patients had varying lengths of follow-up as some died and others had carotid endarterectomy during the 90-day follow-up period, at which point the data were censored. The crude (unadjusted) risk of stroke was estimated from Kaplan-Meier event-free survival analyses. Stratified Cox proportional hazards regression modeling was used to adjust for differences in patient characteristics among the groups. Adjusted stroke-free survival curves were plotted using product-limit estimates. Differences among the curves were assessed for statistical significance using a likelihood ratio test. Logistic regression analysis was used to adjust the frequency distribution of 90-day Rankin scale scores for differences in pre-morbid Rankin scale scores. Differences among proportions in patient characteristics were assessed for statistical significance using a chi-square test.

6.2. Results

A total of 120 patients were enrolled in this study between May 2002 and May 2004, including 69 (57.5%) TIAs. Five patients had a diagnosis other than

stroke or TIA after review of all information at 3 months. The mean age of the 120 patients was 66.0 years and 75 (62.5%) were male. Among these, 15 patients (12.5%) had a DWI lesion and vessel occlusion on the baseline MR scan (7 middle cerebral artery, 5 internal carotid artery, 1 anterior cerebral artery, and 2 posterior cerebral artery). Of the remaining patients, 54 (45.0%) only had a DWI lesion and 51 (42.5%) had neither. Baseline characteristics are shown in Table 1. The mean time from symptom onset to MR imaging was not significantly different among the groups. Patients with a DWI lesion were significantly more likely to have a TOAST classification of large-artery disease compared to patients without a DWI lesion, especially in the presence of vessel occlusion.

A total of 14 patients had a stroke within 90 days, of which 9 (64.3%) occurred within the first 48 hours. Patients with a DWI lesion were at a higher risk of a stroke during follow-up than patients without a lesion, and highest in the presence of vessel occlusion. The unadjusted Kaplan-Meier 90-day risks were 4.0%, 11.6%, and 40.7%, respectively (logrank p-value < 0.001). Baseline NIHSS score and blood glucose > 7 mmol/L were the only patient characteristics identified to be confounding factors from Table 1. Patients with a NIHSS score of 1, 2, or 3 were 1.7 times more likely to have a stroke than patients with a score of 0 (95% CI: 0.4 to 6.8, p-value = 0.42). Patients with an elevated glucose level were also 1.7 times more likely to have a stroke (95% CI: 0.6 to 5.2, p-value 0.36). Even after adjustment for NIHSS score and elevated glucose in a Cox regression, patients with a DWI lesion remained at increased risk (Figure 8). In comparison to patients without a DWI lesion, patients with a lesion were 2.6 times more likely to have a stroke (95% CI: 0.5 to 13.1, p-value = 0.26), whereas those with a lesion and an occlusion were 8.9

times more likely to have a stroke (95% CI: 1.6 to 49.6, p-value = 0.01). Statistically significant differences among groups (p-value = 0.04) was also observed in terms of 90-day functional dependence and death (Rankin score ≥3). The highest proportion was observed in patients with a DWI lesion and vessel occlusion (Figure 9). Only one patient died during the 90-day follow-up period, and they were in the group with a DWI lesion and no vessel occlusion. Patients with large-artery ischemia were no more likely to have a stroke than those without large-artery ischemia (relative risk = 1.7 times, 95% CI: 0.5 to 5.3, P= 0.39).

Of the 69 patients with DWI lesion, 39 (56.5%) presented with a stroke, compared with 13.7% of 51 patients without a DWI lesion. Therefore, the presence of a DWI lesion was related to whether or not the patient had residual signs at 24 hours (P < 0.001). A total of 12 of the 46 (26.1%) patients with a presenting stroke had a stroke at 90 days compared to 2 of 69 (2.9%) patients who presented with a TIA (p < 0.001)

6.3. CONCLUSIONS

This study prospectively examined the predictive value of DWI lesions in patients presenting acutely with non-disabling cerebral ischaemic events (TIA or minor stroke). Patients with a DWI lesion were at a higher risk of a stroke during follow-up than patients without a lesion, and this was highest in the presence of vessel occlusion. This was clinically significant since functional dependence was predicted by the presence of a DWI lesion and vessel occlusion.

Similar to others[36,37,38] we found that that the high-risk period is within the first 48 hours after the initial event, with 64.3% of events occurring during this period. However, we enriched our population because our inclusion criteria utilized

some of the important clinical features associated with increased risk of new stroke (motor or speech deficits). Similar to others we found that an elevated blood sugar confers a higher risk of recurrent events[13]. However, we did not find large artery disease[37] to be predictive of risk, although large artery disease is in the causal chain since it was highly predictive of a DWI positive patient.

Our results show that the longer symptoms are present, the more likely a patient is to have a recurrent event. However waiting for symptoms to resolve is not practical particularly as the clinical diagnosis of TIA versus stroke is inaccurate[134] even by neurologists. With most of the new strokes occurring within the first 48 hours waiting to see if all the symptoms resolve at 24 hours is not practical since interventions will likely need to be instituted promptly. Admitting all TIAs is prohibitively expensive,[135] therefore some means of discriminating patients at high immediate risk at the time they are seen is desirable. A recent proposal suggested a redefinition of TIA as a brief episode of neurologic dysfunction presumptively caused by focal brain or retinal ischaemia without neuroimaging evidence of acute infarction.[39] Our study provides further evidence to suggest that clinical TIA syndromes can be differentiated by acute neuroimaging, rather than by an arbitrary time definition.[136] Others[137] have also found that DWI lesions can predict further vascular events. However this study was performed late with the majority of patients being imaged later than 48 hours after their event. With approximately 50%[13] of recurrent events occurring in the first 48 hours after symptoms any imaging abnormalities seen in these patients may actually be from recurrent events.

There has been previous work examining the role of both CT and MRI as imaging strategies in this patient group. Recent work with computed tomography

(CT) brain scans has shown that evidence of a new infarct on brain CT done within 48 hours of onset in TIA patients is associated with an increased short-term risk for stroke, but did not relate this to functional outcome.[138] Furthermore, brain CT is insensitive to small volumes of injury and the proportion of new infarcts seen on CT among TIA patients is substantially less than that seen on DWI.[139,140] The use of DWI has drawn attention to the high rate of new silent infarcts in stroke patients.[141] However, no study has examined a reliable imaging finding (DWI lesion) in non-disabling cerebral ischaemic events.

The group with the highest rate of new strokes was that with evidence of a vessel occlusion and a DWI lesion. A high proportion (26.7%) of these patients are dependent at 3 month follow up. This appears to be a high risk population and potentially is a target for future therapeutic interventions. It must be emphasized that although a significant minority do poorly, nearly three quarters do well implying that any therapies must have minimal risk of adverse effects.

TIA or minor stroke patients without DWI lesions represent a group with a more benign prognosis. A proportion of these patients may have had a non-ischaemic event of epileptic, migrainous or somatoform origin. These patients were all seen by stroke neurologists who felt the diagnosis was vascular in origin. In our study in only 5 patients did the diagnosis change on review of all the available information at 3 months. The sensitivity and specificity of DWI for acute ischaemic stroke is estimated to be 90%[142,143,144] but caution is needed in assuming that a DWI negative study completely rules out ischaemia. Slice thickness, in plane spatial resolution, artifact from bone, air and CSF may reduce the conspicuity of or mask the appearance of a stroke lesion. There is evidence supporting the notion that a small

subset of patients with clinical strokes are DWI negative,[145] particularly involving the brainstem.[146] The sensitivity and specificity of DWI for acute ischaemic stroke is estimated to be 90%.

This study has limitations. All imaging was performed using the increased magnetic field strength of 3 Tesla. This may enhance detection of ischaemia using DWI sequences by an improved signal to noise ratio[147]. Similar improvements in DWI lesion detection can be achieved with more commonly available 1.5 Tesla strength using sequences with higher resolution and higher signal to noise ratios.[40] Our definition of new stroke was designed to identify a functional deterioration. Clearly both an evolution of the original event causing progression of symptoms (for example, lacunar disease) and a new lesion (for example re-embolization from heart or large artery) would be included in such a definition. Clinical progression is often difficult to differentiate from recurrence. Ideally a follow up MRI using strict definitions for either process could differentiate the two. We did not mandate a follow up MRI, but observe that from a patients perspective all that matters is a deterioration in functional status.

In summary, the presence of a DWI lesion on an MRI in patients presenting acutely with a non disabling deficit is indicative of an increased risk of new stroke within 90 days. The risk is even greater in the presence of a vessel occlusion as well. The presence of a DWI lesion is also predictive of subsequent functional dependence. Acute MRI is useful in making a triage decision for patients with TIA or minor stroke. This needs further validation in independent cohorts.

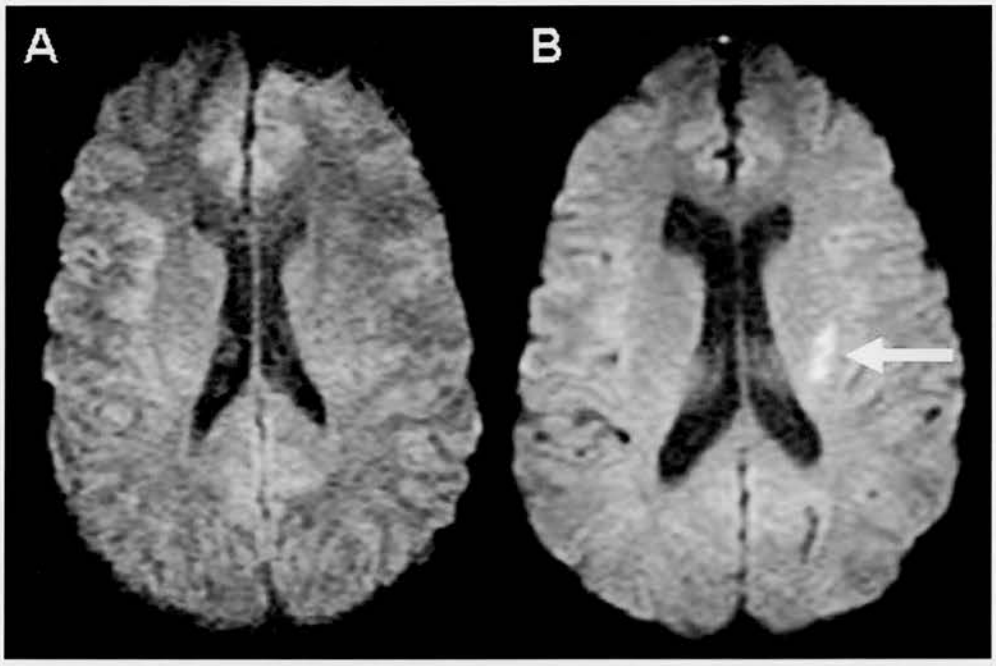


Figure 7: A shows an example of a patient with a DWI negative scan. B shows an example of a patient with a DWI positive scan. The white arrow identifies the DWI hyperintensity.

	DWI Absent Occlusion Absent (N = 51)	DWI Present Occlusion Absent (N = 54)	DWI Present Occlusion Present (N = 15)	P-value
			percent of group	
Age > 60 years*	66.7	70.4	73.3	0.86
Male sex	62.7	61.1	66.7	0.92
Taking antiplatelet medication	29.4	18.5	26.7	0.42
Blood glucose > 7 mmol/L	17.7	2.2	53.3	0.02
Systolic blood pressure > 160mmHg	37.3	40.7	46.7	0.80
Current smoker	13.7	20.4	20.0	0.65
History of:				
TIA or stroke	25.5	20.4	33.3	0.56
Hypertension	49.0	53.7	73.3	0.25
Diabetes mellitus	5.9	16.7	26.7	0.07
Ischaemic heart disease	15.7	14.8	6.7	0.67
Atrial fibrillation	11.8	7.4	6.7	0.70
Hyperlipidemia	23.5	25.9	13.3	0.59
Premorbid mRS 1 or 2 (not 0)	7.8	14.8	26.7	0.15
NIHSS score 1, 2, or 3 (not 0)	39.2	63.0	86.7	0.002
Symptoms to MR imaging > 12 hours†	39.2	33.3	20.0	0.38
TOAST large-artery disease	7.8	25.9	53.3	< 0.001

TIA = transient ischaemic attack; NIHSS = NIH stroke scale; MR = magnetic resonance, mRS = modified Rankin Scale.

* Mean (SD) age of patients: 65.2 (14.5), 66.1 (14.3), and 68.1 (12.4) years, respectively.

† Mean (SD) time interval from symptoms to MR: 10.6 (6.7), 9.4 (5.2), and 7.7 (5.0) hours, respectively.

Table 1. Characteristics of Patients According to Presence and Absence of DWI Lesion and vessel occlusion

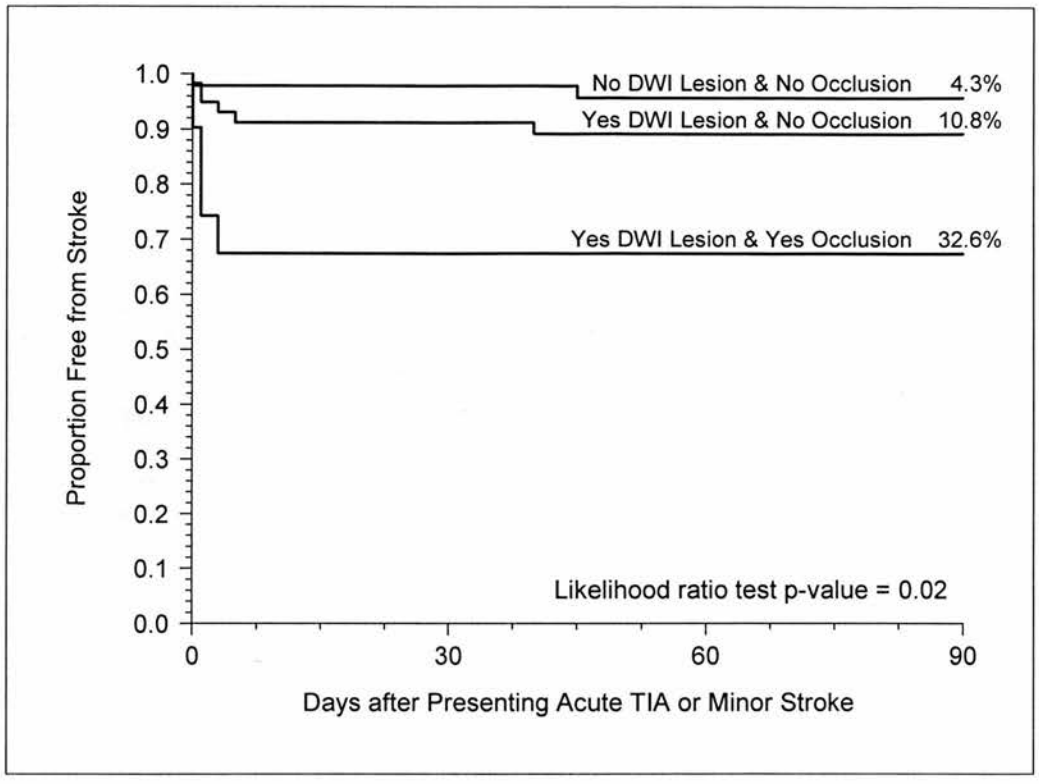


Figure 8: Stroke-free survival curves for patients with and without DWI lesion and total occlusion, adjusted for NIHSS score and baseline glucose level. The adjusted risks of stroke at 90 days are shown as percentages on the right-hand side above the curves.

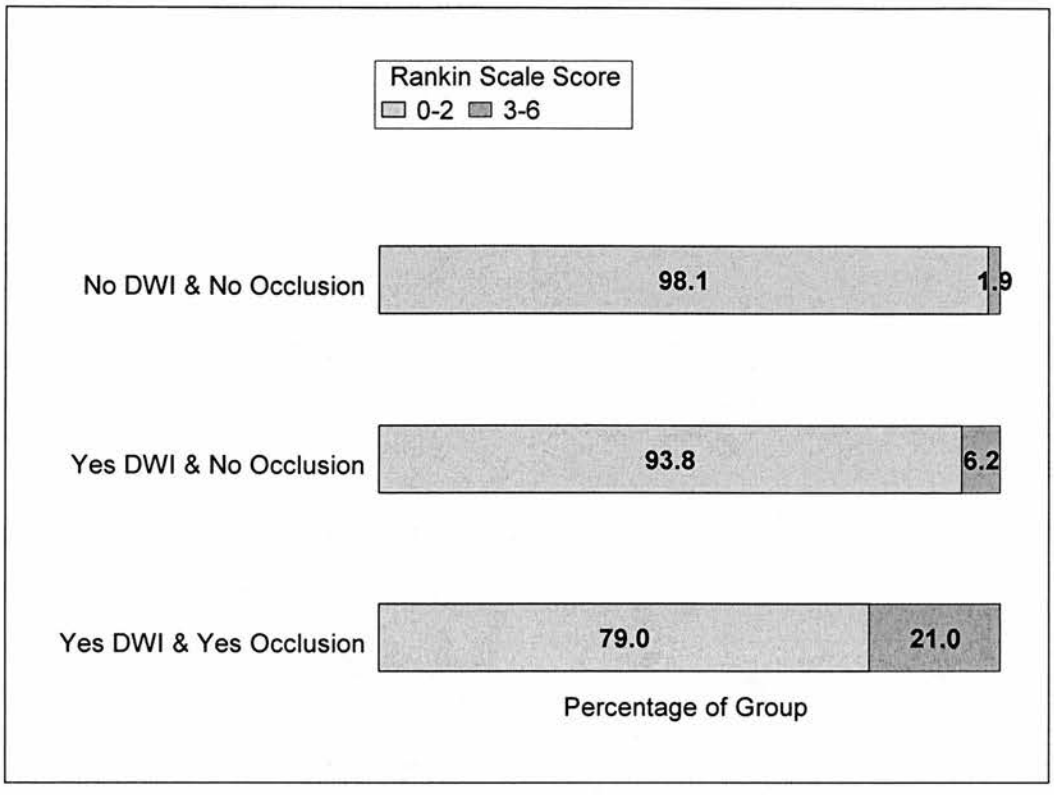


Figure 9: 90-Day Modified Rankin scale scores of Patients enrolled with or without DWI Lesion and total occlusion present on Baseline MRI, adjusted for pre-morbid Rankin scores.

7. Chapter 7: Mild neurological symptoms despite middle cerebral artery occlusion

Recent work suggests that absent middle cerebral artery (MCA) flow signal on MRI correlates with poor clinical outcome[148]. We assessed whether the presence of MCA flow abnormalities among mild stroke patients identified a subset of patients that might deteriorate and be suitable for reperfusion strategies.

7.1. Subjects and Methods

Sequential patients with symptoms of an acute stroke were prospectively included if they had both a CT scan competed in under 6 hours and a MR scan within 7 hours of onset. Exclusion criteria were the presence of cerebral hemorrhage, pre-existing significant non-ischaemic neurological deficits or non-stroke diagnosis. Demographic data, stroke risk factors, and baseline National Institutes of Health Stroke Scale (NIHSS) were recorded prospectively by a stroke neurologist or trained stroke nurse. Mild neurological symptoms were defined as a NIHSS score of three or less. The outcome measures were defined by the Rankin scale at three months, categorized into independence (0 to 2), dependence (3 to 5), and death. We identified patients with transient or minor neurological deficits (an NIHSS $\leq$ three) and evidence of a MCA occlusion on 3D time-of-flight MR angiography (MRA) at baseline.

MR images, obtained using a 3-Tesla scanner (Signa; GE Medical Systems, Waukesha, WI) equipped with high performance gradients (40mT/m, 184-μs rise time), and using a standard quadrature head coil, included sagittal T1, axial T2, axial FLAIR, DWI, perfusion weighted (PWI) and 3D time-of-flight MR angiography (MRA) and 3D time-of-flight MR angiography (MRA) post gadolinium.[130] One stroke neurologist experienced at interpreting MRA, blinded to all clinical

information except symptom side, assessed the MRA in the anterior circulation for areas of reduced or absent flow signal in the distal internal carotid artery (ICA) and MCA. The MRA flow signal abnormality was categorized as: none, involving distal ICA, M1-MCA, M2-MCA or distal MCA.

One stroke neurologist retrospectively analyzed the images blind to clinical details and outcomes, looking for evidence of DWI/PWI mismatch, defined as present if the estimated volume of a PWI–abnormality was greater than the DWI-abnormality volume. Matching DWI and PWI images were placed on the MR workstation simultaneously. Functool (Functool 2000 User Guide, General Electric Medical Systems) was used to create the perfusion maps. A PWI abnormality was present if there was any visible abnormality on the relative mean transit time map when viewed on grey scale.

Data are reported in frequency tables. Proportions were compared using Fisher's exact test, continuous variables with a Student's t-test and ordinal variables with a Mann-Whitney-U test as appropriate. All tests were two-sided and conventional levels of statistical significance at 5% were used.

7.2. Results

A total of 106 consecutive patients were included between October 1999 to July 2001. MR was commenced within the three hours of onset in 42% of patients and 79% of patients underwent CT scanning within three hours of symptom onset. An MRA was completed in 104 patients and 49 of these had evidence of flow abnormalities. Five patients were identified with both a NIHSS score of three or less (NIHSS$\leq$3) and isolated flow abnormalities seen on MRA in the MCA (two M1-MCA, three M2-MCA; see Figure 10 for an example) consistent with vessel

occlusion. None of these five patients had symptoms suggestive of a lacunar syndrome. Four of the five patients had evidence of DWI changes on MR. Of the other 101 patients, 28 had NIHSS>3 and flow abnormalities on MRA in the MCA without coincident ICA occlusion. All of the 28 patients with MCA occlusion and NIHSS>3 had evidence of a DWI lesion at baseline. These two groups of patients (MCA occlusion + NIHSS>3 and MCA occlusion + NIHSS <3) were analyzed separately (Table 2). There was no statistical difference in the proportion of patients who had CT or MRI within three hours of symptom onset, nor in the hemisphere of stroke between the NIHSS <3 with MCA occlusion group (n=5), and the NIHSS>3 with MCA occlusion group (n=28).

All five patients in the NIHSS ≤ 3 and MCA occlusion group were right hand dominant and none of them of received thrombolytic therapy. One patient deteriorated by two points on the NIHSS score in the first 24 hours, but all five were independent on the modified Rankin Score at three months. See Table 3. All patients with NIHSS<3 and MCA occlusion had a 30-day NIHSS that was less than or equal to their admission score. In contrast, among patients with NIHSS> 3 and MCA occlusion, 54% were dead or dependent at ninety days (p=0.09).

Two patients had a repeat MRA at 24 hours and both had evidence of persistent occlusion. Five NIHSS <3 with MCA occlusion patients had perfusion-weighted imaging performed on the acute MR scan and 2 patients had evidence of a mismatch between DWI and PWI. There was no statistical difference between presence of mismatch in the NIHSS <3 with MCA occlusion patients (n=5); and the NIHSS>3 and MCA occlusion patients (n=24).

7.3. Discussion

Persistent ischaemia in the absence of a severe neurological deficit has been previously suggested using delayed SPECT.[149] It is important to note that one patient (20%) fluctuated neurologically, but all five were independent at follow-up. These patients were all seen by the acute stroke team, considered for thrombolytic therapy and not treated because of mild symptoms. The good prognosis in our study is important because MCA occlusion and good prognosis have not been previously associated. However, we advise caution at over interpretation of these results on the basis of this small sample. All patients had evidence of a stroke on imaging in the appropriate vascular territory that the vessel occlusion was seen. However we can not rule out the possibility that some of these occlusions were chronic. If this were the case it may bias our results towards good outcome.

With the increasing availability of non-invasive imaging, we routinely have information about the site of vascular occlusion but do not have empiric evidence to guide translation of that information into effective clinical decisions. Most physicians would not offer thrombolysis to patients with mild stroke symptoms due to their expected good prognosis, but in the NINDS tPA stroke study[7] there were patients with as low a NIHSS as 1 included. Although we know that "mild" patients can deteriorate[12] our experience suggests that despite vascular occlusion, these patients may not be the population of stroke patients that deteriorate and need thrombolytic therapy.

Vascular occlusion plays a major role in the prognosis of acute ischaemic stroke, but the effect is likely mitigated by compensatory collateral blood flow. None

of our patients recanalized within 24 hours suggesting that collateral flow remains important for hours to days. The experience documented in the EC-IC bypass study emphasizes this concept[150]. Reduced collateral blood flow assessed on CTA[76] has previously been shown to identify those at risk for infarct expansion. In the setting of MCA occlusion with mild symptoms, good control of blood pressure with fluid replacement or even induced hypertension may be beneficial[151] by improving collateral flow. A clinically useful tool to measure collateral blood flow might allow stratification of patients with vascular occlusion into those who require reperfusion and those who do not.

PET studies in primates and humans support the concept of perfusion thresholds that predict early, late or no subsequent infarction[152]. Analogous information is beginning to emerge using multimodal stroke MRI,[153] but perfusion MR currently only provides semi-quantitative data. Mismatch between PWI and DWI has been proposed as a tool that identifies patients who are at risk of deterioration and have potentially salvageable brain tissue.[24] Post-hoc analysis suggests that patients with PWI-DWI mismatch do not uniformly do badly[101]. Absolute quantification of blood flow using MR may be crucial to predict patient outcome by allowing the clinician to visualize tissue at risk of infarction.
Further study using neuroimaging is needed to understand mechanisms for clinical deterioration and recurrent stroke in the mild stroke and TIA population[39]. We suggest caution in recommending thrombolysis to patients with a mild symptoms and MCA occlusion.

	NIHSS≤3 + MCA occlusion (n=5)	NIHSS>3 + MCA occlusion (n=28)
Mean Age	64.3	65.5
Median NIHSS	3	16
tPA - iv or ia	0	15
Number of males	4	20
Left side of body event	3	10
Mean Initial blood glucose	8.3	6.8
Mismatch on MR	2	6 (n=24)
M1-MCA occlusions	2	16
M2-MA occlusions	3	12

Table 2: Demographic characteristics of NIHSS < 3 + MCA occlusion group compared to the group of patients with NIHSS>3 + MCA occlusions. None of the comparisons were statistically significant.

	NIHSS baseline	24hr NIHSS	30 Day NIHSS	Hemi-sphere	3 month modified Rankin	Site of Vessel occlusion	Follow-up MRA
1	3	1	0	Right	Independent	M2	No recan-alization
2	2	0	0	Right	Independent	M2	utd
3	2	4	1	Left	Independent	M1	utd
4	3	3	2	Right	Independent	M1	No recan-alization
5	3	1	0	Left	Independent	M2	utd

Table 3: Breakdown of five patients with NIHSS≤3 and MCA occlusion.

UTD = unable to determine.

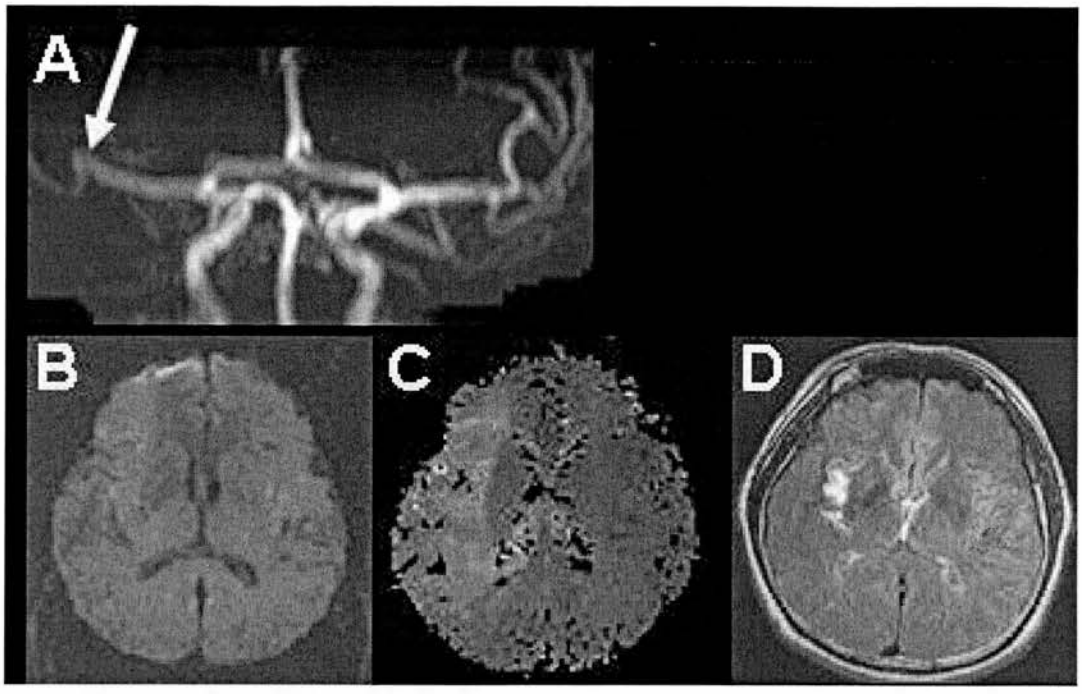


Figure 10: Case 4. 60 year old man who developed left sided weakness and dysarthria. He improved en-route to hospital and on arrival in the ER he had a NIHSS of three. MRA showed attenuated flow (white arrow) at the MCA bifurcation (A) with complete occlusion of the superior M2 division and diminished flow in the inferior M2 division. His DWI imaging initially showed no evidence of a lesion. (B). PWI showed a large area of Mean Transit Time (MTT) delay (C). He had a fluctuating clinical course over the next 24-48 hours, with a NIHSS varying between three and six. He was treated with volume therapy, did not deteriorate further and at 30 days had a follow up scan. FLAIR (D) shows right insular infarction. He was functionally independent and had a NIHSS of two.

8. Chapter 8: Silent Ischaemia in Minor Stroke and TIA patients identified on MR imaging

Many studies have shown a high incidence of recurrent events in minor stroke and TIA patients.[13] Recent work has shown that in a general population of stroke patients admitted to one hospital the rate of new lesions seen on MRI at 1 week as compared to the baseline scan was much higher than expected.[140] It was also found that many of these events were clinically silent. The population studied included patients that were treated with thrombolysis or had evidence of a perfusion abnormality on their baseline MRI. We sought to determine if the same risk applied to patients with TIA or minor stroke. Further, we explored predictors of new lesion development on follow-up MRI.

8.1. Methods

8.1.1. Subjects

In a prospective study of TIA and stroke patients presenting to a tertiary referral centre within 12 hours of symptom onset, we examined patients with an NIHSS<6 at baseline who were imaged with a 3T MRI at baseline and at 30 days. This cut off was used since at out institution most patients with a deficit at this level would not normally be treated with tPA. Follow up imaging was reviewed for evidence of any new ischaemic lesions distinct from the original infarct, as compared to the baseline MR. Demographic data were collected including whether iv tPa was given, glucose, BP, history of hypertension, atrial fibrillation, smoker, diabetes and valvular heart disease. Any new clinical strokes were recorded and the date of the event was also recorded. Patients were treated acutely with tPa if the treating physician wished to do so and secondary prevention with anti-platelet agents was left

at the discretion of the attending neurologist; however, routine treatment at our center includes treatment of hypertension, use of antiplatelet therapy or anticoagulant therapy, treatment of hyperlipidemia with statin agents and dietary and lifestyle counseling.

8.1.2. Imaging

Images were obtained using a 3-Tesla scanner (Signa; GE Medical Systems, Waukesha, WI) equipped with high performance gradients (40mT/m, 184-μs rise time), using a standard quadrature head coil. Acute imaging sequences included DWI (isotropic b = 0 and 1000 s/mm2, TR = 7000 ms, TE = 96.5 ms), PWI (TR = 2250, 1750 and 1850 ms; TE = 40, 45 and 45 ms; flip angle = 45°; 26, 51 and 42 repetitions), sagittal T1, axial T2, axial FLAIR, 3D time-of-flight MR angiography (MRA) of the intracranial circulation and ADC maps were calculated from the DWI with the General Electric workstation.[130] The changes in the PWI were due to sequence optimization and corresponded to the acquisition of 19, 10 and 12 slices, respectively. All images were acquired with a 320 mm field of view with 5.0 mm slice thickness and 2.0 mm gap. The images were reconstructed to dimensions of 256 x 256 voxels. Mean transit time (MTT) maps were calculated from the concentration-time curves obtained from the PWI series.

Imaging was assessed by a neuroradiologist blind to all clinical information other than symptom side and any subsequent imaging information if applicable. The MR sequences were examined for the presence of an acute stroke lesion on the baseline MRI. If there was a lesion present this was further classified into whether there was a solitary lesion or multiple. The MTT map was examined for any delays in perfusion. Any delay in mean transit time as compared to the opposite side was

considered abnormal. The MRA and post gadolinium MRA; source images and MIP's were examined for evidence of any flow voids consistent with vessel occlusion. The 30 day follow up MRI was rated with the acute MRI scan visible simultaneously. Any new lesion outside the original DWI lesion was rated as being a new lesion. The simple expansion of the baseline DWI lesion was not regarded as being a new lesion. In some cases this was difficult to assess and therefore a consensus was reached between 3 raters (1 neuroradiologist and 2 stroke Neurologists). New lesions were further stratified into; 1.new lesion within the baseline perfusion abnormality; and 2. new lesion outside the original perfusion abnormality.

8.1.3. Clinical follow up

Patients were examined at the time of their 30day MRI scan blind to their imaging results and the QVFVS[109] was used to identify any recurrent events that had not been known to the investigator previously. The patients were also reviewed at 3 months at which time their final clinical assessment was made. NIHSS, modified Rankin Score and Barthel scales were all completed at 30days and at 3 months. At 3 months the TOAST[133] classification was identified for each patient: 1. large artery atherosclerosis; 2. Cardio-embolism; 3. Small vessel occlusion, 4. Stroke of other determined cause and 5. stroke of undetermined cause. Each patients chart was reviewed by 1 individual and every recurrent event and TOAST criteria was double checked. Any patients in whom there were discrepancies between the clinical information and the collected research information were reviewed and a consensus was reached.

8.1.4. Statistics

The data are described using simple descriptive statistics. Proportions were assessed using the Fisher's exact test or Chi square test as appropriate. A Chi square test for trend was used to assess 2 x n contingency tables. Comparisons among groups were made using one-way ANOVA or the Kruskal-Wallis test. Within ANOVA, comparisons were adjusted using the Bonferonni method. Logistic regression analysis was used to assess the association between presence of new lesions on MRI and clinical and MR factors.

8.2. Results

The total number of patients meeting the entry criteria was 143 and these were enrolled between May 2002 and February 2004. 65 patients were classified as having had a TIA as per the classical definition,[129] the median NIHSS was 2 (interquartile range (IQR) 0-3) and 56 patients were female (39.2%). 29 patients (16.9% (29 out of a potential 172 patients who had a baseline MRI completed) were excluded from the study due to the 30 day MR not being completed (reasons included; lost to follow up, claustrophobia, cardiac valve inserted etc.). 7 patients (4.9%) were treated with intravenous tPA. The median time to baseline MR scan was 8.5 hours (IQR 4.8-15.8 hours). The median time from symptom onset to follow up MR was 29 days (IQR 26-32 days). 46 patients (32.1%) had no evidence of a DWI lesion on their baseline MRI scan; 71 patients (49.7%) had evidence of a solitary lesion on baseline MRI and 26 patients (18.2%) had multiple lesions on their MRI. Table 4 shows the clinical characteristics for each group. Diabetes and large artery disease were more likely in the group with multiple baseline lesions.

14 patients (9.8% CI_{95} 5.5-15.9) had MR evidence of recurrent lesions on their MRI at 30days. 10 of these patients (71.4%) had new lesions outside the original area of perfusion abnormality (as defined by the MTT map). Of these recurrent lesions 6 were clinically asymptomatic (42.9%); 6 had new strokes (42.9%) and in two patients (14.2%) symptoms appeared to be explained by progression in the first 24 hours of their stroke (both these patients had recurrent lesions in the area of original perfusion abnormality). In one TIA patient the baseline MR showed no DWI abnormality, however the follow up scan showed a new DWI lesion that had been clinically silent. Figures 11 and 12 show examples of patients' who had new MR lesions seen on 30day follow up MRI.

In univariable analysis, elevated baseline glucose (OR 1.26 per mM increase in baseline glucose, CI_{95} 1.0-1.6, p=0.034) and diabetes (OR 3.2 CI_{95} 0.97-10.6, p=0.056) were associated with new lesions on MRI at 30 days. A trend to increased likelihood of new lesions at 30 days was seen with progressing baseline scan lesion number (none, solitary, multiple: p=0.046). The absolute increase in risk of a new MRI stroke at 30 days was 11.2% (CI_{95} 3.2-19.2, RR = 6.2) with any baseline DWI lesion. When grouped together, patients with large artery disease or cardioembolic causes of TIA or minor stroke were more likely to have recurrent events on MRI at 30 days compared to other stroke types (RR= 2.9 CI_{95} 1.0-8.4, p=0.043). In a multivariable model adjusting for age, baseline serum glucose and increasing lesion number were associated with new MRI lesions at 30 days, but these results were not statistically significant at $p<0.05$.

8.3. Discussion

Recurrence of ischaemia as defined by MRI was reasonably frequent (9.8%) in our sample despite the fact that the patients had only mild or no clinical deficits at the time of enrolment. We found that almost half of these lesions were clinically asymptomatic. The only factors in our study predictive of recurrent ischaemic lesions were the number of baseline lesions and baseline serum glucose. This seems intuitive in that if you have more lesions at baseline you are likely at higher risk for recurrent lesions. In support of this, other groups have found that multiple lesions at baseline on MRI predict recurrent clinical events.[154]

Our study differed from that by Kang et.al. [141]in that they found the rate of any recurrent lesions to be 34%. One reason for this is that the populations of patients are different; we examined only mild stroke and TIA patients (NIHSS<6). In their study they looked at all patients in a general hospital and many of the patients had severe strokes. However the approximately 10% risk of a recurrent ischaemic lesion shows that minor stroke and TIA not only have a high risk of clinical strokes,[13] but also of accumulating silent ischaemia. Although the risk of recurrent imaging ischaemia was less than in previous studies, the amount of silent ischaemia was high at around 46%. Previous studies have suggested that the rates of clinical recurrence after all types of stroke is between 3.3% to 6% in 30days[155,156] and this is consistent with our results. This is important since it suggests that despite best medical secondary prevention these patients are still at risk of recurrent ischaemia. Patients presenting with "mild" clinical events are at significant risk of on-going cerebral ischaemic damage. Other than the risk of a clinical symptomatic stroke, there appears to be other risks with the accumulation of silent ischaemia. This is one

of the proposed mechanisms for cognitive decline in patients with high grade asymptomatic carotid disease.[157]

There have been many publications on the high risk of recurrent clinical events in TIA[13,35,36,37,38] and minor stroke patients, however none of them have looked at recurrent imaging events. New events on MR are more frequent than clinical events and thus may be useful as a surrogate outcome for acute stroke prevention trials. This is a strategy which has proved very successful in identifying treatment response in multiple sclerosis.[158,159] It may be possible in the future to monitor a patients MRI scan for evidence of active disease since this appears to be more sensitive than waiting for clinical recurrent disease. There is little evidence currently to say definitively that recurrent MR lesions that are clinically silent are a negative thing. However there is emerging evidence that clinically silent recurrent infarcts on MRI are however associated with cognitive decline.[160,161] Our study found the only risk factor for recurrence of ischaemic lesions on MRI was multiple lesions on the baseline MRI. Like others we showed that large artery disease and cardioembolic mechanisms are associated with an increased risk.[141,38]

In conclusion minor stroke and TIA are associated with a 10% risk of recurrent events based on imaging, however this is much lower than is seen in more severely affected patients. Patients with multiple lesions at baseline are at an increased risk for recurrent imaging ischaemia.

	No DWI lesion (n=46)	Single DWI lesion (n=70)	Multiple DWI lesions (n=26)	p
Age (median, iqr)	73.5 (58-78)	69.5 (60-76)	69.5 (59-76)	0.720
Female Gender	39%	43%	31%	0.583
NIHSS (median, iqr)	0 (0-2)	2 (0-3)	2 (1-3)	0.078*
Diabetes	7%	18%	31%	0.028**
Atrial fib	15%	4%	15%	0.070**
Hypertension	54%	61%	58%	0.788**
Current Smoker	13%	20%	31%	0.194**
Ischaemic heart dx	17%	15%	8%	0.573**
Glucose (mM)	6.2 (1.3)	6.6 (2.2)	7.8 (2.1)	0.004†
MAP (mmHg)	108 (17)	108 (15)	113 (18)	0.301†
TOAST				0.064‡
Large artery	8.7%	21.1%	34.6%	
Cardioembolic	19.6%	18.3%	15.4%	
Small vessel	13.0%	18.3%	7.7%	
Other determined	0%	5.6%	0%	
Undetermined	58.7%	36.6%	42.3%	

*Kruskal-Wallis test.
**Fisher's exact test
†Oneway anova. In post-hoc comparison between groups, glucose was higher in the multiple DWI lesion group compared to both solitary DWI lesion group (P=0.024) and to no DWI lesion group (P=0.003) after Bonferonni adjustment.
‡Chi square test

Table 4: Comparison of the demographics of minor stroke patients (NIHSS<6) depending on the presence of no DWI, single or multiple DWI lesions.

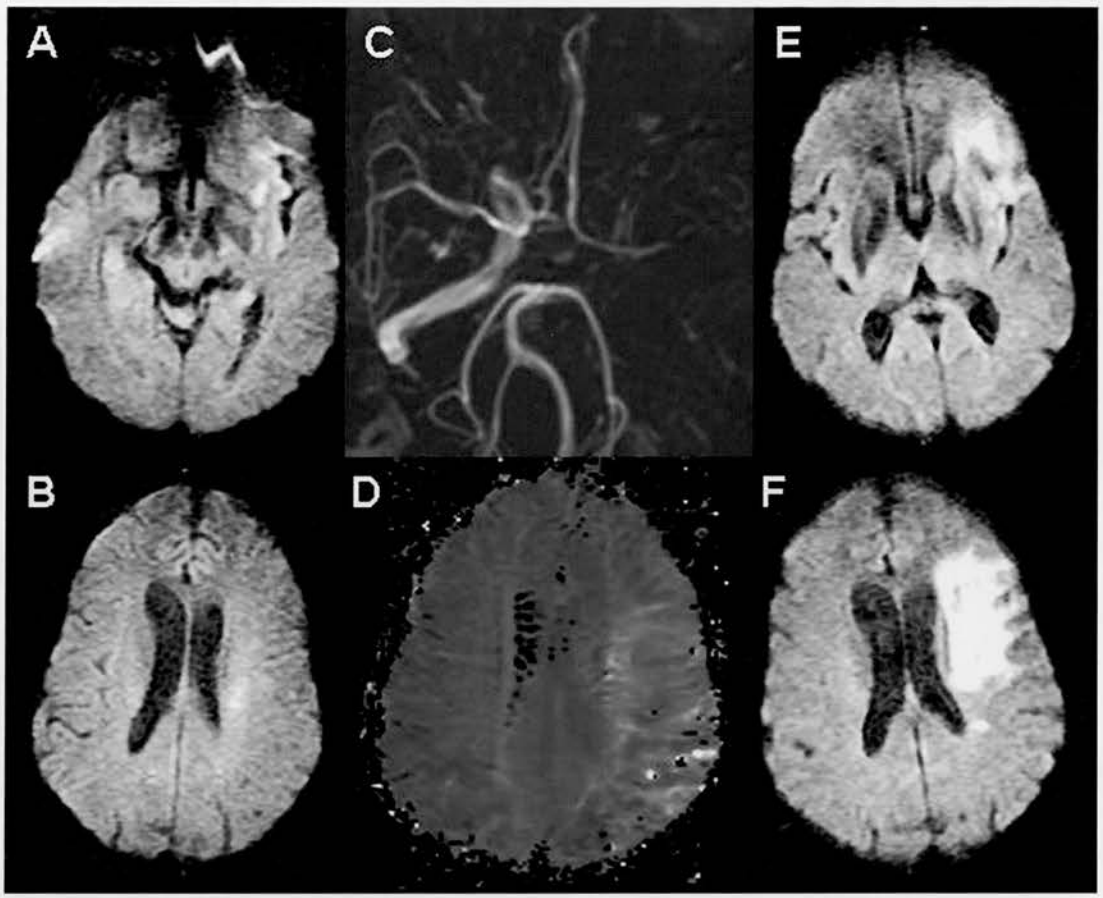


Figure 11: A, B, C and D show the baseline MRI of a 79 year old female with a left ICA and M1 occlusion, with initially a small DWI lesion. She presented with a baseline NIHSS of 2 consisting of mild right sided weakness and progressed to severe right hemiparesis. 12 hours after admission to hospital. The MTT map showed only a mild MTT abnormality, but it was larger than the DWI lesion. E and F show the 30day DWI scan with a new DWI lesion in the same vascular territory, but outside the original perfusion abnormality.

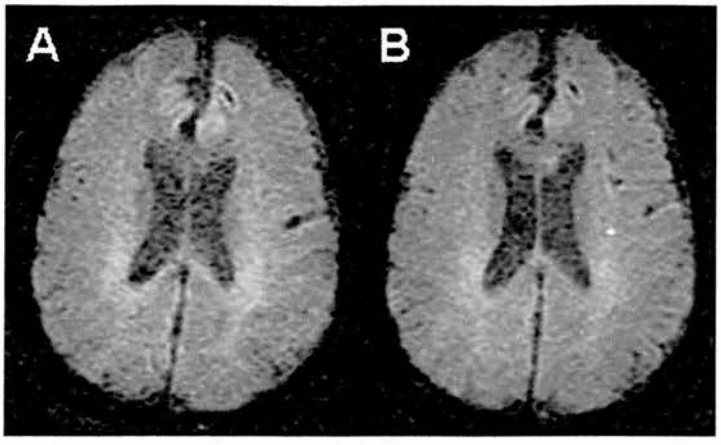


Figure 12: A. Normal scan at baseline (no DWI lesion seen, no vessel occlusion and no perfusion abnormality) in a 79 year old male patient with a left hemispheric TIA lasting 90 minutes – B. The patient remained clinically asymptomatic. B shows a small new DWI lesion in left MCA territory seen at 30days on follow up MR.

9. Chapter 9: A high proportion of TIA patients show perfusion abnormalities despite resolution of symptoms

Many patients with TIA, according to this classical definition, have injury observed on diffusion weighted imaging (DWI) of the brain.[41,42,43,44,45] The assumption that TIAs are associated with complete resolution of brain ischaemia leaving no permanent brain injury[39,40] is clearly not true. There is growing evidence that TIA is not a benign condition and the substantial risk of a subsequent stroke after a TIA urges prompt evaluation so preventative measures may be taken.[3,4,13] The risk of a disabling stroke is high within the first 48 hours after the initial event[13] suggesting that TIA is an unstable condition. Persistent ischaemia in the absence of symptoms is one potential mechanism for recurrent stroke after TIA. In this prospective study we sought to see if MRI perfusion abnormalities exist early in TIA patients despite the rapid resolution of symptoms.

9.1. METHODS

We prospectively enrolled consecutive patients greater than 18 years old presenting to Foothills Medical Centre with symptoms of a TIA consisting of hemiparesis or aphasia (speech or motor deficits) examined within 12 hours of symptom onset. Our institutional ethics committee approved the research protocol and proper written informed consent was obtained. Demographic information and clinical history was obtained at the time of the arrival to the emergency room. A stroke neurologist examined all patients included in the study. TIA was clinically defined using the World Health Organization (WHO) definition[129], as rapidly developed clinical signs of focal or global disturbance lasting fewer than 24 hours, with no apparent nonvascular cause. TIA was confirmed by a stroke neurologist 24

hours post symptoms if all symptoms had resolved. The amount of time until symptom resolution was documented.

9.1.1. Imaging

MR imaging was performed as soon as possible after arrival in the emergency department and within 24 hours of symptom onset. Images were obtained using a 3-Tesla scanner (Signa; GE Medical Systems, Waukesha, WI) equipped with high performance gradients (40mT/m, 184-μs rise time), using a standard quadrature head coil. Acute imaging sequences included DWI (isotropic b = 0 and 1000 s/mm2, TR = 7000 ms, TE = 96.5 ms), PWI (TR = 2250, 1750 and 1850 ms; TE = 40, 45 and 45 ms; flip angle = 45°; 26, 51 and 42 repetitions), sagittal T1, axial T2, axial FLAIR, 3D time-of-flight MR angiography (MRA) of the intracranial circulation and ADC maps were calculated from the DWI with the General Electric workstation[130]. The changes in the PWI were due to sequence optimization and corresponded to the acquisition of 19, 10 and 12 slices, respectively. All images were acquired with a 320 mm field of view with 5.0 mm slice thickness and 2.0 mm gap. The images were reconstructed to dimensions of 256 x 256 voxels. Mean transit time (MTT) maps were calculated from the concentration-time curves obtained from the PWI series.

9.1.2. Image interpretation

Imaging was assessed by a neuroradiologist blind to all clinical information other than symptom side and any subsequent imaging information if applicable. Images were all examined on 2 large 23inch monitors. Contrast was allowed to be altered to emphasize differences between tissues. The images were examined for the

presence of an acute DWI lesion; none, solitary and multiple. The MTT map was examined for the presence of a perfusion delay and then the 2 series were examined for the presence of mismatch (MTT abnormality>DWI lesion), matched deficits (MTT=DWI) and reverse mismatch (DWI>MTT). The MRA of the circle of Willis – pre and post Gadolinium; MIP's and source images were examined for evidence of a flow void consistent with a vessel occlusion.

9.1.3. Patient Outcomes

Patients had a neurological assessment at 24 hours and at 3 months after their presenting event to the emergency department. The National Institutes of Health Stroke Scale (NIHSS)[106], modified Rankin scale[131,132] and the Questionnaire to validate stroke-free status (QVSFS)[109] were completed by the neurologist at 3 months. At 3 months, after reviewing all clinical and imaging information, the final diagnosis of the presenting event was made and the potential mechanism assigned using the TOAST[133] classification.

9.1.4. Statistics

Patient characteristics are shown using standard descriptive statistics. The association between the presence or absence of a rMTT delay (PWI lesion) was assessed for all baseline characteristics. Logistic regression modeling using backward elimination was used to identify predictors of a PWI lesion. Only a main effects model is presented because of the relatively small cohort.

9.2. RESULTS

A total of 69 classical TIA patients were enrolled between May 2002 and December 2003. Median duration of symptoms was 90 minutes (range 5-1380 minutes). 27 patients were female (39%). In 56 of the patients (81%) the symptoms had resolved by the time of the beginning of the MRI scan.

In 7 (10.1%) patients who had an MRI performed the PWI sequence was not completed or was not able to be interpreted due to movement artefact or other technical difficulties. These patients were included in the analysis of patients without a PWI lesion. In 21(33.9%) patients there was evidence of a delay in the MTT map. See results in table 5. Mean time to MRI scan was 9.2 hours in patients with a PWI lesion and was 13.6 hours in patients without a PWI lesion (p=0.04).

In 12 patients (57.1%) this perfusion abnormality was present despite having their neurological symptoms completely resolved (see figure 13). In 14 patients (66.7%) who had MTT abnormalities seen there was a larger area of MTT delay than the size of the DWI lesion (mismatch).

In a multivariable model, occlusion is the most important predictor of PWI lesion or not (p=0.011). This is true even after accounting for time and whether the patient has clinically resolved or not.

Nearly all patients (66/69, 95%) had a modified Rankin score (mRS) of 0 or 1 at 3 months. Of the three patients who had a mRS > 1, all had resolved clinically by the time of the MRI scan but two had a persistent PWI abnormality. Two of these patients had recurrent strokes (one who had a PWI abnormality and one who did not). Among patients with complete clinical resolution of symptoms at the time of MRI, 21% had a PWI lesion.

9.3. DISCUSSION

In this study we have found that despite many patients having transient symptoms a significant proportion of TIA patients have perfusion abnormalities evident on MRI (as defined by the MTT map). The only factor to be predictive of a perfusion abnormality in a multivariable analysis was the presence of a vessel occlusion on MRA.

Previous work imaging TIA patients within the first month after their symptoms using SPECT[162] has shown that despite the event being relatively distant most of the patients had some abnormality in perfusion or in their response to acetazolamide. The authors concluded that these patients may be at risk for sub-clinical ischaemia. There is also a case series reported where 3 patients with completely resolved TIA's were given a midazolam challenge and their neurological deficits returned.[163] One explanation for the recurrence in symptoms would be persistent sub-clinical ischaemia. No perfusion studies were performed in this case series. There is growing evidence that TIA is not a benign condition especially in the first 48 hours after the event. The presence of persistent ischaemia in the absence of symptoms is one possible mechanism for recurrent stroke after TIA.

In our analysis we found that vessel occlusion was the only factor that predicted the presence of a PWI lesion and that this was not necessarily correlated with the clinical assessment of symptom resolution. Work described in Chapter 7[164] has suggested that patients can have mild neurological symptoms in the presence of a middle cerebral artery occlusion and still achieve good neurological outcomes. Similarly, in this study nearly all patients had an excellent outcome. This is different

than much of the previous literature. One major difference in this study is that all patients were admitted to hospital and were seen by a stroke neurologist at baseline, 24 hours and at any neurological deterioration. This meant that the diagnosis of TIA or stroke was as correct as it could be and patients with minimal symptoms that might be considered normal by a non stroke expert were not classified as a TIA. This may be the reason for the low event rate in these patients.

Importantly, a discord between clinical complete resolution and the presence of a PWI abnormality was observed in this study. Further study using quantitative perfusion techniques[165] to define benign oligemia[166] is required to determine if symptom resolution is associated with benign oligemia alone and therefore could be used to differentiate tissue at risk of infarction.

There are limitations to our study. This was performed at 3 Tesla and with the higher signal to noise ratio theoretically we may identify more areas of subtle abnormality than if the studies had been done at 1.5T. We also used the MTT map and this parameter can overestimate the amount of tissue at risk in a given patient.[167] Some other groups have used thresholding techniques when looking at the MTT map. We felt that any evidence of perfusion abnormality in this population of patients was of interest.

Although these patients were scanned quickly, in most patients their neurological deficits had completely resolved by the time of scanning. It is well known that patients with severe carotid stenosis can have MTT delays on imaging; however this does not appear to be the only explanation for these deficits since many of these patients did not have evidence of large artery disease. It is also theoretically possible that the prolonged MTT seen in these patients is caused by metabolic

depression. The delay to MR scanning was longer in TIA patients whose scans to not show evidence of a PWI abnormality suggesting that the proportion of TIA patients with perfusion abnormalities may well be much higher. The delay to MR scanning was longer in TIA patients whose scans did not show evidence of a PWI abnormality suggesting that our results may underestimate the true proportion of TIA patients with perfusion abnormalities.

In a high proportion of TIA patients there is evidence of persistent active disease by way of perfusion abnormalities despite the rapid resolution of symptoms.

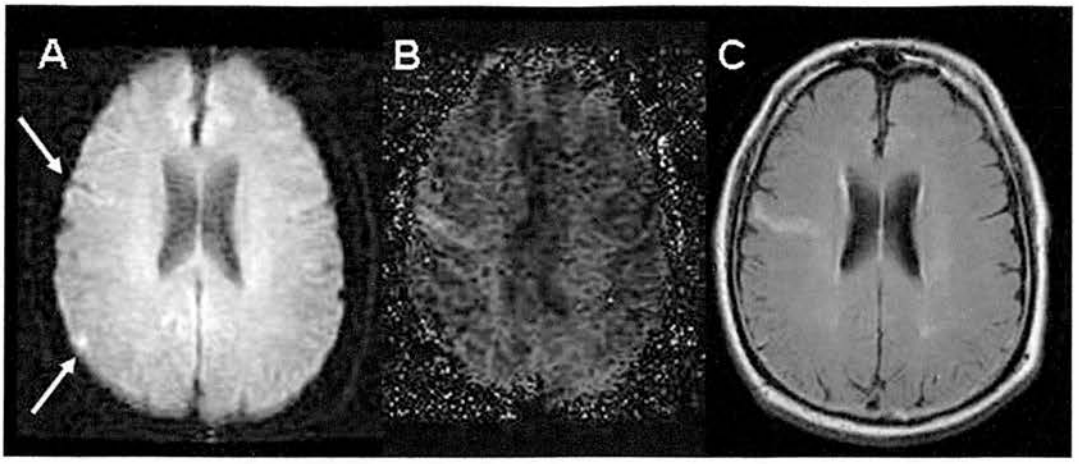


Figure 13: A. DWI lesions shown by arrows at baseline in a TIA patient whose symptoms of left sided weakness resolved within 30 minutes. B. shows the MTT abnormality at baseline. C. hyperintense region in right MCA territory on the FLAIR at 30 days. This is in the area of the abnormal perfusion abnormality at baseline. The patient was clinically asymptomatic.

	PWI lesion (n=21)	No PWI lesion (n=48)	
Age	69 (12)	67 (12)	0.35
Male gender	52%	65%	0.43
NIHSS (median)	0 (0 – 1)	0 (0 – 0.5)	0.23
Onset-to-MRI time	552 (103)	817 (72)	0.04
ICA disease	14%	2%	0.081
Resolved	57%	92%	0.002
Occlusion	48%	8%	<0.001

Table 5: Comparison of clinical factors in patients with PWI lesions and those who do not have evidence of PWI lesion (univariable analysis). The last column shows p values. Variables (age, gender, blood pressure, baseline serum glucose, baseline NIHSS score, diabetes mellitus, atrial fibrillation, ischaemic heart disease, cholesterol, antiplatelet treatment, past stroke or TIA, smoking status) that were not significant at $p < 0.05$ are not shown.

10. Chapter 10: Discussion and summary

10.1. ASPECTS; a rating scale for acute ischaemic changes, can be reliably interpreted by experienced physicians in real time.

Since the publication of the NINDS tPA trial in 1995[7] and licensing of tPA in North America the treatment of stroke as an acute medical emergency has blossomed. Initially the non contrast CT was used to screen patients for evidence of hemorrhage only. Technology has advanced and the state of the art CT scanners in use in large centres can give images minutes after the patient arrives in the emergency room. Not all patients benefit from tPA and indeed some suffer harm. Thus many stroke physicians have tried to find ways to refine the current criteria for thrombolysis. The European Co-operative Acute Stroke Study (ECASS) trials[59] identified the importance of early ischaemic change seen on CT in predicting benefit with intravenous thrombolysis. Patients were eligible only if there was ischaemia involving less than one third of the middle cerebral artery (MCA) distribution territory. This method has proved not to be reliable and the Alberta Stroke Program Early CT Score (ASPECTS) was developed by the team here in Calgary to attempt to reliably quantify ischaemic changes. ASPECTS has been shown to predict functional outcome and the risk of symptomatic hemorrhage in tPA treated stroke patients.[65] However, the ability to reliably identify ischaemic changes on CT in real time is a more difficult task than that performed in a perfect research environment. In Chapter 3 we show that ASPECTS is reliable when performed in real time by a group of individuals experienced in scoring ASPECTS. The reliability is good, but not

excellent however, even in experienced hands. This perhaps emphasizes the difficulty in basing any treatment decisions on a particular ASPECTS score.

10.2. ASPECTS can be applied to the CTA-SI in acute stroke and identifies more abnormal tissue than the NCCT alone.

Until recently ASPECTS has been a scale for assessing ischaemic change on the NCCT in acute stroke. Recently it has been applied to MRI's performed in acute stroke - DWI[113] and PWI[168]. In Chapter 4 we show that ASPECTS can be applied to CTA-SI reliably and that on average more damage is identified. Unfortunately the numbers were too small to look at response to treatment in patients who have a large mismatch between the NCCT ASPECTS and the CTA-SI ASPECTS. This is an important area since CT Angiography is much more widely available than MRI.

10.3. ASPECTS on CTA-SI may be useful in patients with a normal NCCT.

The usefulness of early ischaemic changes in acute stroke appears to be twofold. Firstly, the use of early CT changes can help reduce the risk of symptomatic intracranial hemorrhage with tPA treatment if you withhold treatment from those with extensive ischaemic damage. There is also however a proportion of patients who present with one of the many "stroke mimics" (e.g. seizure, migraine, functional etc.) and sometimes a completely normal scan can leave the physician with diagnostic uncertainty. In this case further neurovascular imaging can be useful. There are a variety of ways that the diagnosis of acute ischaemic stroke can be confirmed. Transcranial Doppler (TCD) could be used to identify an occluded vessel,

MRI if available quickly could be used to screen for stroke or as we have shown CT Angiography can be helpful. The advantages of CTA in acute stroke is that it is fast, cheap and the images are able to be interpreted immediately. In Chapter 4 we show that CTA-SI can help identify the presence of hypoperfusion confirming a stroke in a number of cases where the NCCT was considered normal. This may be especially of help in smaller centres where the expertise at interpreting acute ischaemic changes may not be as prevalent.

10.4. Estimating mismatch between DWI and PWI with the human eye is not reliable

In chapter 5 we found that quantifying mismatch by the human eye is reproducible, but not reliable among observers. This has implications for basing any potential treatments based on this method. The error that we found in this study was around ± 20% making any treatment decisions made on a certain percentage of mismatch problematic. This would potentially be a major problem if the late treatment of patients without a certain percentage mismatch would increase the rate of hemorrhage. Further research is needed in this area and trials such as EPITHET[95] may answer some of the uncertainties.

10.5. TIA and Minor stroke patients can be triaged with an acute MRI scan performed in the first 24 hours.

Patients who have completely resolved or who have minimal symptoms seem the perfect target for secondary prevention. However despite current best medical therapy a substantial proportion of minor stroke and TIA patients will go on to have a stroke within the next 90 days[13] In Chapter 6 we show that 50 % of patients do not have any evidence of an acute DWI lesion on an acute DWI-MRI. These patients are at a low risk of having a recurrent stroke. It is not cost effective or efficient to admit all TIA and minor stroke patients to hospital for investigation and treatment. This result if confirmed may allow many patients to be discharged home and investigated as an in- patient. We also discovered that patients with evidence of a DWI lesion and a vessel occlusion were at a very high risk of recurrent events (around 30%). Further secondary prevention trials should possibly concentrate only on patients with evidence of ischaemia on MRI. It may actually be that a substantial proportion of DWI negative patients do not have any ischaemia to begin with.

10.6. Do the results from Chapter 6 and 7 contradict each other?

About a third of patients who have thrombolytic therapy withheld because of initially mild symptoms have been found to be dead or dependent at 3 month follow up/discharge.[12] The work in chapters 6 and 7 addressed this issue and asked the question whether acute imaging of the cerebral arteries using MRI helps to predict which patients are likely to deteriorate or have a further event. In chapter 7 we studied 5 patients with acute stroke and mild symptoms (NIHSS ≤ 3) in whom MRI scan showed a middle cerebral artery occlusion, a group anecdotally felt to be at high

risk of deterioration if no recanalization is obtained. None of the patients were treated with thrombolysis and yet all were independent at 3 months. On the other hand, in chapter 6 we studied 15 patients with minor stroke or TIA who on MRI had both a DWI lesion and evidence of a vessel occlusion, and showed that by 3 months around 40% had had a recurrent event and 4 (27%) were dead or dependent. Part of the explanation for these seemingly different findings may be that the populations studied were different. In chapter 7, we studied only patients with MCA occlusion whilst in chapter 6 we also included patients with ICA, ACA and PCA occlusion (There were 15 patients with vessel occlusion; 7 of which were MCA occlusions (3 M1 occlusions and 4 M2 branch occlusions), the other vessel occlusions included 5 ICA, 1 ACA and 2 PCA's). However, 3 (43%) of the 7 patients in chapter 6 who had MCA occlusions were dead or dependent at 3 months. We do not have recanalization data on most of these patients at 24 hours so cannot comment on whether vessel recanalization led to good outcome. Lastly, it must also remain possible that the optimistic results of chapter 7 – that no patients with mild symptoms and an MCA occlusion were dead or dependent - were a chance finding due to the small number of patients studied. Regardless of the explanation, it is important to note that 4 (57%) of the 7 patients with MCA occlusion in chapter 6 were independent at 3 months. Taken with the findings of chapter 7, it therefore still seems reasonable to conclude that, for many patients with minor stroke or TIA and MCA occlusion, the prognosis remains surprisingly good. The question that remains is how to identify which patients are likely to do well and which are likely to do badly. This would allow potential therapies to be established to prevent poor outcome. If we could identify which patients in this population are likely to have a

poor prognosis then potentially thrombolysis with tPA or even novel therapies may be offered to these patients.

10.7. TIA and Minor stroke patients have a high rate of clinically silent recurrent ischaemic lesions

Previous work looking at a cohort of all stroke patients admitted to a general hospital showed an unexpectedly high rate of recurrent ischaemia.[141] This work suggests that despite current methods for secondary prevention stroke patients still have a high risk of ischaemia. In Chapter 8 we looked at a different population of patients - TIA and mild stroke patients. We found a much lower rate than Kang et al did suggesting that the populations of patients may be different. However the rate of around 10% is still significant, especially in these patients with such mild symptoms. Further secondary prevention trials need completed to reduce the accumulation of ischaemic disease. Importantly we found that patients with multiple baseline lesions had a higher risk of recurrent ischaemic lesions. These patients are at high risk for recurrent ischaemia and clearly need further treatment than the current standard of care.

10.8. A high proportion of TIA patients show perfusion abnormalities despite resolution of symptoms

It is now well known that patients with TIA's are at high risk for recurrent events. We found in chapter 9 that despite most of these patients having completely resolved in terms of their symptoms in a surprisingly high proportion of patients

there was evidence of ongoing perfusion abnormalities. This was seemingly unrelated to large artery disease, although the numbers are small. Importantly, a discord between clinical complete resolution and the presence of a PWI abnormality was observed. Further study using quantitative perfusion techniques is required to determine if symptom resolution is associated with benign oligemia alone. Potentially, quantitative perfusion techniques could be used to differentiate tissue at risk of infarction from tissue that is not.

There are many potential mechanisms for recurrent stroke including re-embolisation, complete occlusion, and other hemodynamic factors etc. This work further emphasises that there is a subgroup of TIA patients who have truly active disease. This seems comparable to unstable angina in the cardiology world. Further research is needed to clarify whether these patients are at increased risk for recurrent events.

10.9. The use of MR imaging for clinical trial enrolment

There is much interest at the moment into optimising anti-platelet therapy in stroke prevention. Results from the CURE[169] trial where the addition of clopidogrel to standard therapy with aspirin showed benefit in reducing recurrent events. Recent results from the MATCH trial[170] showed a non-significant difference in reducing vascular events, but the risk of major bleeding was increased. It may be possible using MR imaging to identify patients for future stroke prevention trials. For example only TIA and minor stroke patients with evidence of a DWI lesion at baseline could be enrolled, thereby not exposing low risk patients to possible harm. Recurrent lesions seen on follow up MRI may also be used as a marker for treatment

effect. The continued accumulation of ischaemic disease may require more intensive therapy (with statins, antihypertensives etc.).

10.10. Summary

Acute stroke and TIA patients are a diverse group of patients and new imaging techniques are being used to identify patients at risk for recurrent events and/or response to thrombolysis.

ASPECTS is a rating scale for ischaemia in the middle cerebral artery territory and has been used until now with studies completed retrospectively or with consensus scores. We showed that ASPECTS can be rated by an experienced group of raters reliably in real time. This is important since a scale is not useful in clinical practice unless it is reliable in real time and not just in a research setting. ASPECTS was also reliable when applied to CTA-SI. ASPECTS performed on CTA-SI identified more evidence of ischaemic change than the NCCT alone. This may be helpful in identifying populations for thrombolysis.

Minor stroke and TIA are not benign conditions. The presence of an acute DWI lesion on MRI heralds patients at high risk for recurrent events and functional dependence. We also found that some patients with vessel occlusion and minor stroke and TIA are at high risk of a poor outcome. However, interestingly these are a surprising number of patients with minor stroke and vessel occlusion who have a good outcome. Follow up MRI also can identify patients who are accumulating ischaemic damage despite best medical therapy. Despite minor symptoms these patients have a 10% risk of new ischaemia as seen on MRI at 1 month, around 50% of these ischaemic events are clinically asymptomatic. MR Imaging of TIA has

showed that approximately 50% of these patients have evidence of ischaemic damage despite resolution of symptoms. We looked at perfusion imaging in TIA patients and found that many patients had evidence of perfusion abnormalities despite resolution of symptoms. Further work is necessary to see the clinical implication of this.

CT and MR Imaging in acute stroke and TIA patients can identify new potential populations of patients for future therapeutic trials of stroke prevention and treatment.

Consent Form

This consent form, a copy of which has been given to you, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

INTRODUCTION

The Acute Stroke Team in Calgary comprised of investigators from the Calgary Health Region and the University of Calgary is conducting studies involving diagnostic imaging in acute stroke. Described below are the tests that may be performed while you are in hospital. You are being asked to allow investigators at the University of Calgary and the Calgary Health Region to perform these tests and have access to the images and your health records to collect information that may be helpful in the understanding of acute stroke. The studies are complementary to regular care and may aid in the understanding of your stroke. Each study may or may not benefit your immediate care. Each carries minimal or no risk to you. Please review the consent form below with us.

1. 3 Tesla Magnetic Resonance Imaging (3T MRI)

1.1. Introduction

MRI provides a safe, non-invasive method of obtaining diagnostic information about the structure and function of any designated part of the body, in this case the brain. The purpose of the 3T MR study is to determine if MR imaging helps in the treatment of acute stroke patients.

1.2. Procedures

The 3T MR Study involves baseline imaging as soon as possible after stroke onset. Additional scans may be suggested as part of a serial follow up study, which may include a

repeat scan following your stroke. Each time a series of MR images will be taken which could include non-standard imaging sequences. Routinely a contrast agent (gadolinium) is given by intravenous injection to better visualize structures in the brain. Which could include non-standard imaging sequences.

1.3. Risks and Discomforts

There are no known long-term effects from MR. MR machines use strong magnets to take pictures, if you have an implanted pacemaker or other metal device, you are unable to go in a MR machine. You will be carefully screened for this and we will also ask you to remove your watch, any hearing aid and other metal items. A very small minority (less than 1%) of patients will experience mild tingling, muscle twitching, or claustrophobia. Very rarely, a patient will experience an allergic reaction to the contrast agent. Commonly such reactions are mild and do not require treatment. Extremely rarely, they are life threatening and require intensive treatment.

2. **Transcranial Doppler Ultrasound (TCD)**

2.1. Introduction

Occlusion of the arteries in the brain is the most common cause of stroke. Ultrasound imaging may be used to obtain information on the flow of blood within the brain. The purpose of the TCD project is to determine if TCD helps in the treatment of acute stroke patients.

TCD is an approved technique in Canada and the United States. TCD provides a safe, non-invasive method of obtaining diagnostic imaging about the brain's arteries.

2.2 Procedures

The TCD will be done as soon as possible after the onset of your stroke symptoms. A TCD examination takes approximately 15 minutes. An ultrasound probe is placed on your head while you lie on a bed or sit in a chair. Where indicated, additional exams or continuous monitoring may be suggested as part of the study.

2.3 Risks and Discomforts

There are no known harmful effects or discomfort associated with this technology.

3. **Computed Tomographic Contrast Studies–Angiography (CTA) and Perfusion (CTP)**

3.1 Introduction

CT Angiography and CT Perfusion provides a safe, non-invasive method of obtaining blood flow in the arteries of the brain in relation to possible brain death associated with lack of blood flow. CT Angiography gives information about which blood vessels are affected by the stroke. CT Perfusion gives us absolute measurements of blood flow to various portions of the brain. This assists radiologists in analysing blood flow of stroke victims—where the speed of diagnosis and treatment is often the primary factor in determining the extent of recovery. CT Perfusion generates colour images that allow physicians to evaluate the extent of brain tissue damage quickly and to plan treatment. CT Perfusion has received approval for clinical use.

3.2 Procedures

After the standard CT of the brain, a bolus of intravenous contrast is given to the patient (in the absence of any contraindications). The head is scanned again to develop pictures of the blood vessels supplying the brain. This CT Angiography can give us information into which blood vessels are blocked. If it is felt clinically relevant a second bolus of contrast will be administered and the area of brain of interest will be scanned. This CT Perfusion study will give us absolute levels of blood flow to various areas of the brain.

3.3 Risks and Discomforts

Some patients may experience mild side effects, which usually pass quickly but may last a few minutes. Mild side effects may include warmth, burning sensation, nausea, vomiting, taste alteration, hives and itching. These usually require no treatment or respond quickly to medication. In rare occasions, life threatening or even fatal reactions may occur.

There is an increased dose of radiation used with CT Angiography and Perfusion as compared to a normal CT scan. The risk from the increased dose of radiation is very small.

4. VISION – Vascular Imaging of acute Stroke for Identifying predictors of clinical Outcome and recurrent ischaemic eveNts

4.1. Introduction

VISION is a comparison research study investigating three neurovascular imaging methods: Magnetic Resonance Imaging (MRI); Computed Tomography (CT) and Transcranial Doppler (TCD) ultrasound. The objective of the study is to determine which combination of imaging modalities (tests) should be used in various clinical situations allowing for the most optimal (successful) outcome. You will be one of approximately 720 patients participating in this study. Your clinical participation in the study will last approximately 90 days.

4.2. Procedures

You will receive the same standard care given to all stroke patients including a careful physical examination. Your doctor will determine medications and tests used for you standard care.

All baseline imaging will be completed as soon as possible after stroke onset. If you agree to participate in this study and you meet all of the entry criteria, your doctor will continue to collect information about you during your hospitalisation, and for approximately 90 days after your stroke. Most of the information collected will be performed during the first 24 hours of this study. Additional MRI/CT scans or TCD may be performed. You will be asked to return for follow up visits at 30 (+/-14) days and 90 (+/-14) days after your stroke. During each evaluation a

series of neurological exams will be performed. Baseline imaging may include 2 or more modalities to be determined by the treating physician:

Clinical Follow Up

Baseline:	Possible Additional Scan:	1 month:	3 month:
3T MRI/CT/TCD/CTA/CTP	3T MRI/ CT/TCD	3T MRI or CT (if unable to complete MRI)	physician assessments

Telephone Follow Up

6 months	1 year	18 months	2 years

A Study Nurse or Study Investigator will call you by telephone after you are home. You will be asked questions if you have experienced any new stroke/TIA symptoms. These phone calls will take approximately 5-10 minutes each, and would take place at 6 months, 12 months, 18 months and 2 years.

4.3. Risks and Discomforts

Please see risks described in sections 1.3, 2.3, and 3.3.

5. **MONITOR**- Modelling the EvolutiON of Infarcting Tissue in the setting of Occlusion and Recanalization

5.1. Introduction

MONITOR is a research study investigating brain lesion evolution (change) and outcomes between patients who have recanalization (opening of the artery) and those who have no recanalization of the MCA occlusion (blockage). The ultimate aim is to develop imaging indicators, which will help identify stroke patients who could benefit from treatment interventions. You will be one of approximately 24 patients participating in this study. Your participation in this study will last approximately 90 days.

5.2. Procedures

You will have already received diagnostic imaging of the brain (CT and MRI) and brief sound wave ultrasound test of the blood vessels (arteries) in the brain (TCD) to determine that he blockage is located in the middle cerebral artery (MCA).

Additional MRI/CT scans or TCD may be performed 12 (+/- 6) hours, 24(+/-6) hours, 7(+/-2) days, and 30(+/-10) days following your stroke. Routinely a contrast agent (gadolinium) is given by intravenous injection to better visualise the structures in the brain. Each scan takes about 30 minutes.

A TCD examination will be done as soon as possible after the onset of your stroke symptoms and lasts for 15 minutes. In some cases, a lightweight head frame will be positioned using Velcro and a knob for adjusting allowing for repeated exams every 30 minutes for up to 8 hours after stroke onset. The head frame will be loosened between examinations. Repeat TCD exams will be performed after the 12 and 24 hour MRI studies.

If you agree to participate in this study and you meet all entry criteria, your doctor will continue to collect information about you during your hospitalization and for approximately 90

days after your stroke. Most of the information will be collected during the first 24 hours of this study. You will be asked to return for follow up visits at 7(+/-2) days, 30(+/-14) days and 90 (+/-14) days after your stroke. During each evaluation a series of neurological exams will be performed.

5.3. Risks and Discomforts

Please see risks described in sections 1.3, 2.3, 3.3.

6. **Serial CTP**- Development of CT based Indices of Tissue Viability and Infarction in Acute Stroke

6.1. Introduction

Serial CTP is a research study that involves CT scanning and measuring brain blood flow and brain blood volume in stroke patients. The objective of the study is to investigate whether measuring brain blood volume and brain blood flow will help predict patient clinical outcome. You will one of 80 patients participating in this study. Your participation in this study will last approximately 7days.

6.2 Procedures

You will receive the same standard of care that is given to all stroke patients including a careful physical examination. You will have already received diagnostic imaging of the brain (CT and/or MRI) on admission to the hospital.

Additional CT scans at 24 (+/-6) hours and 7 (+/-3) days will be performed following your stroke. The head is scanned again to develop pictures of the blood vessels supplying the brain. This can give us information into which blood vessels are blocked. You will receive a bolus of intravenous contrast (in absence of any contraindications). Each CT scan takes approximately 10 minutes to perform. If you agree to participate in this study, and meet all the entry criteria, your doctor will continue to collect information for 7 days during your hospitalisation. You will not have to return for follow up visits as part of the study, but you will need to return as part of your care after your stroke at 90 days.

Baseline:	24hours:	7days:
3T MRI/CT/TCD/CTA/CTP	CT: +/- CTP/CTA scan	CTscan: +/- CTP/CTA

6.3-Risks and Discomforts

Please see risks described in sections 1.3, 2.3, 3.3

7. **ONO-2506 MRI Substudy**

Primary Investigator: **Dr Michael Hill, Tel (403) 944-8065**
Study Sponsor: **Ono Pharma USA, Inc.**

7.1. Introduction

To participate in the ONO-2506 MRI Substudy you must have provided informed consent for the main ONO-2506 Study (Protocol # 2506/INT0104). If you choose to participate in the MRI Substudy, two special MRIs will be performed during the Evaluation Phase (on Study Day 1) and again approximately one-month later (at the study site). The purpose of this Substudy is to

assess the differences between 1.5T and 3.0T stroke MRI among patients randomized to the ONO trial. There will be a total of 10 patients enrolled at this site.

7.2 Procedures

Evaluation Phase (on Study Day 1):

If you are eligible to enter the study, you will be randomly assigned (like flipping a coin) to one of two groups. You will receive either a 1.5T stroke MRI first or a 3.0T stroke MRI first immediately followed by a second stroke MRI on the other magnet or shortly after the first intravenous infusion of the investigational medication. All patients would therefore have both a 1.5T and a 3.0T stroke MRI. Group A would be defined as stroke patients who had 1.5T MRI followed by a 3.0T MRI and group B patients would be defined as patients who had a 3.0T MRI followed by a 1.5T MRI.

Each time a series of MR images will be taken which could include non-standard imaging sequences. Routinely a contrast agent (gadolinium) is given by intravenous injection to better visualize structures in the brain. Which could include non-standard imaging sequences.

Month 1:

You will receive both a 1.5T stroke MRI first and a 3.0T stroke MRI at approximately 1 month following your stroke.

7.3-Risks and Discomforts

Please see risks described in sections 1.3.

8. **CT versus MRI in hemorrhage detection**- The detection of hemorrhagic transformation in acute stroke.

8.1. Introduction

CT vs. MRI is a research study that is evaluating the advantages of Magnetic Resonance (MR) imaging as compared to Computed Tomography (CT) imaging in detecting bleeding (hemorrhage) in the brain following a stroke. This research is trying to determine whether: 1) MR imaging can be used instead of CT to determine blood in the brain following stroke 2) detect leaky blood vessels within the brain at the time of stroke to predict future bleeding. You will be one of 60 patients participating in this study. Your participation in this study will last approximately 72 hours.

8.2 Procedures

You will receive the same standard of care that is given to all stroke patients including a careful physical examination. You will have already received diagnostic imaging of the brain (CT and/or MRI) on admission to the hospital.

You will undergo a repeat CT scan at 72 hours (+/- 24 hours) after your stroke. You will receive intravenous contrast (as long as you have had no reactions to same prior). This will take

approximately 10 minutes. An additional MRI scan will also be performed at 72 hours (+/- 24 hours) following your stroke. This will take approximately 30 minutes to complete. Information will be collected for about 72 hours during your hospitalisation. You will not have to return for follow up visits as part of the study, but you will need to return as part of your care after your stroke at 90 days.

8.3-Risks and Discomforts
Please see risks described in sections 1.3, 2.3, 3.3

PROCEDURES

In addition to standard stroke follow up, you may be asked to return to the hospital for further follow up assessments. This may include a physical/neurological exam; stroke scales and possibly repeat imaging. We will try to coordinate these visits to occur at the same time.

POSSIBLE BENEFITS

The information obtained may be helpful in planning and monitoring your therapy. The study will not affect the quality of your care. Participation may help future patients suffering from stroke.

COMPENSATION

In the event that you suffer as a result of participating in this research the Calgary Health Region, the University of Calgary or the researchers will provide no compensation. You still have all your legal rights. Nothing said here about treatment or compensation in any way alters your right to recover damages.

VOLUNTARY PARTICIPATION

Your participation in these research studies is voluntary. You can decide not to participate, and you are free to withdraw from this study at any time without penalty or loss of benefits and your withdrawal will not jeopardise your medical care at this facility. You may also decide to participate in only parts of this series of diagnostic studies.

INFORMATION COLLECTED

The information (clinical and imaging) collected will remain confidential in the hands of the investigators.

The images collected through this research will be stored confidentially in a computerized database that is protected by a "firewall". A database allows researchers to assess the information collected at a later time for further analysis and secondary publications to help

expand the knowledge bases regarding stroke. You have the right to contact the researchers at any point in time and have your images and information removed from the database. Also, in the event of your death, your next of kin may also request to have your images deleted and destroyed.

The results of these studies may be presented at meetings or in publications; however, your identification will not be disclosed. Images may be used by industry but your identification will be kept confidential. None of the investigators have a financial conflict of interest in asking you to participate.

CONSENT

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In particular, you have understood to your satisfaction the study purpose, risks and benefits, how the information will be used and that you are under no obligation to participate and may withdraw at any time.

In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardising your health care. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. If you have further questions concerning matters related to this consent form, please contact:

3T MRI, CTA and CTP: Dr. Robert Sevick @ (403) 944-1800
TCD: Dr. Andrew Demchuk @ (403) 944-8287

If you have any questions concerning your rights as a possible participant in this research, please contact Pat Evans, Associate Director, Internal Awards, Research Services, University of Calgary at (403) 220-3782.

I wish to have the following tests:

θ 3T MRI	θ CTA	θ VISION	θ Serial CTP study	θCTvs.MRI
θ TCD	θ CTP	θ MONITOR	θ ONO-2506 MRI Substudy	hemorrhage detection

1. PATIENT OR SURROGATE/LEGAL GUARDIAN

_____ _____/_____/20__
Participant's signature day month

calgary health region

UNIVERSITY OF CALGARY

Foothills Medical Centre

_____	_____	_____	_____/_____/20__
Surrogate's signature	Name	Relationship	day month

2. INVESTIGATOR

I certify that I have explained the above procedure(s) and in my opinion, _____, understands its nature, risks and consequences.

_____	_____	_____/_____/20__
Investigator or Delegate's signature	Name	day month

3. WITNESS

_____	_____	_____/_____/20__
Witness' signature	Witness' name	day month

A copy of this consent form will be made available for you.

For Inclusion for Pediatric Studies:

The investigator will, as appropriate, explain to your child the research and his or her involvement, and will seek his or her ongoing cooperation throughout the project.

SURROGATE CONSENT

Because your illness made it impossible for you to participate in the informed consent process, the proxy (delegate) consent of your next of kin (legal surrogate or guardian) was obtained on your behalf. Your surrogate believed you would have wished to participate in this research if you had been able to express your own opinion at the beginning of the research.

As noted earlier, the process of informed consent must be continuous throughout a research project. This means that patients have the right to change their minds and, therefore, must be given opportunities to voice any changes they might wish. In your situation, you now have the opportunity to agree or disagree with the decision made by your surrogate to enroll you in this project.

If you agree with the decision made by your surrogate to enroll you, your signature will affirm your participation in this study. If you do not agree with the decision made by your surrogate to enroll you, you may withdraw at anytime from the study.

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the

study at any time without jeopardizing your health care. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation.

Please check the appropriate box(es) to indicate your decision:

- ❑ I do agree with my surrogate's decision
- ❑ I do not agree with my surrogate's decision
- ❑ I wish to remain in the study
- ❑ I wish to withdraw from the study

_____		_____/_____/20__
Patient's Signature		DD/MM/YY
_____	_____	____/_____/20__
Witness' Signature	Witness' name	DD/MM/YY

A copy of this consent form will be made available for you.

Appendix 2 : Patient characteristics/ baseline characteristics

Patient #	**FMC-** _ _ _	Name:	
Patient FHH#		Date of event	____ / ____ / _____ dd mmm yyyy
Patient PPR#		Time of event onset	_____h
AHCIP #		Time of ER arrival	_____h
Patient Initials	— — —	INR in ER _____	Blood Glucose in ER _____
Gender	☐ M ☐ F	Plts in ER_____	Admission ASPECTS ____
DOB	____ / ____ / _____ dd mmm yyyy	Handedness: ☐ Right ☐ Left	BP in ER triage ____/____
Treated with IV rtPA ☐ yes ☐ no Weight____ __kg	Time started _____h Dose of IV tPA = ____mg ☐ 0.9 mg/kg or π 0.6 mg/kg	Treated with IA rtPA ☐ yes ☐ no	Time started_____h Dose of IA tPA = _____mg

Baseline Hematocrit _____	SymptomSide: ☐Left ☐Right ☐Aphasia	Enrolled in another trial ☐ yes ☐ no	Name of trial:	If TIA, length of symptoms _____

- ☐ Hypertension
- ☐ Atrial fibrillation (at any time)
- ☐ Valvular heart disease
- ☐ Recent MI (<3/12)
- ☐ Known CAD/ischaemic heart dx
- ☐ Known CHF
- ☐ Sub-therapeutic INR
- ☐ On anti-platelet therapy
- ☐ Known carotid disease
- ☐ Current smoker
- ☐ High cholesterol
- ☐ Previous TIA/Stroke ☐ < 3/12
- ☐ Diabetes
- ☐ Allergy to Contrast Dye
- ☐ Patient on Glucophage
- ☐ Renal failure
- ☐ Hx of cancer
- ☐ None of the above

APPENDIX 3: NIH Stroke Scale Patient Initials: _____ FMC #_____

o Baseline	o 24hours (+/- 6 hours from baseline NIHSS)	o 30 days (+/- 2 weeks)	o 3 months (+/- 2 weeks)

1a	**Level of Consciousness:** 0 = Keenly responsive 1 = Not alert, but arousable by minor stimulation to obey, answer or respond 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped) 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid	
1b	**LOC Questions:** 0 = Answers both question correctly 1 = Answers one question 2 = Answers neither question	
1c	**LOC Commands:** 0 = Performs both tasks correctly 1 = Performs one task 2 = Performs neither task	
2	**Best Gaze:** 0 = Normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the occulocephalic maneuver.	
3	**Visual:** 0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)	
4	**Facial Palsy:** 0 = Normal symmetrical movement 1 = Minor paralysis (flattened nasolabial fold, asymmetry of smiling) 2 = Partial paralysis (total or near total paralysis of lower face 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	
5	**Motor Arm:** 0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds 1 = Drift, limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 degrees 3 = No effort against gravity, limb falls 4 = No movement A= Amputation or joint fusion, explain: _____	5a Left: _____ 5b Right _____
6	**Motor Leg:** 0 = No drift, leg holds 30 degrees position for full 5 seconds 1 = Drift, leg falls by the end of the 5 second period but does not hit bed 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity 3 = No effort against gravity, leg falls to bed immediately 4 = No movement A= Amputation or joint fusion, explain: _____	6a Left: _____ 6b Right _____
7	**Limb Ataxia:** 0 = Absent If present circle each limb YES or NO 1 = Present in one limb Right Arm: YES NO Left Arm: YES NO 2 = Present in two limbs Right Leg: YES NO Left Leg: YES NO Amputation or joint fusion, explain: _____	
8	**Sensory:** 0 = Normal; no sensory loss 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but pt is aware 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm & leg	
9	**Best Language:** 0 = No aphasia, normal 1 = Mild to mod aphasia: some obvious loss of fluency or facility of comprehension without significant limitation on ideas expressed or form of expression. 2 = Severe aphasia: all communication is through fragmentary expression; great need for inference, questioning , and guessing by the listener carries burden of communication 3 = Mute, global aphasia; no usable speech or auditory comprehension	
10	**Dysarthria:** 0 = Normal 1 = Mild to mod: patient slurs at least some words and at worst, can be understood with some difficulty 2 = Severe: patient's speech is so slurred as to be unintelligible in the absence of or out or a proportion to any dysphasia, or is mute/anarthric 9 = Intubated or other physical barrier, explain: _____	
11	**Extinction and Inattention (Neglect)** 0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral Simultaneous stimulation in one of the sensory modalities 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space	
12a	**Distal Motor Function: (Arm)** 0 = Normal A = At least some extension after 5 seconds, but not fully extended. Any movement of the Fingers which is not command is not scored B = No voluntary extension after 5 seconds. Movements of the fingers at another time not scored	12a L: _____ 12b R _____
	IF NIHSS = 0, then please document length of symptoms:_____ (at 24hrs only) ****(For 24 hours only)**** **TOTAL:**	

APPENDIX 4 : Modified Rankin Scale and Barthel Index

Modified Rankin Scale Information provided by: _____

o Baseline (pre-stroke)	o 1 month (+/- 2 weeks)	o 3 months (+/- 2 weeks)

o	0 = Asymptomatic
o	1 = No significant disability, despite symptoms; able to carry out all usual duties and activities
o	2 = Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
o	3 = Moderate disability; required some help, but able to walk without assistance.
o	4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
o	5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
o	6 = death

Barthel Index Information provided by: _____

o Baseline (pre-stroke)	o 1 month (+/- 2 weeks)	o 3 months (+/- 2 weeks)

		Score
1. Feeding	0 = unable 5 = needs help cutting, spreading butter etc. 10 = independent	
2. Transfer (bed to chair and back)	0 = unable; no sitting balance 5 = major help (one or two people; physical); can sit 10 = minor help (verbal or physical) 15 = independent	
3. Grooming	0 = needs help with personal care 5 = independent face/hair/teeth/shaving(implements provided)	
4. Toilet Use	0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	
5. Bathing	0 = dependent 5 = independent (or in shower)	
6. Mobility	0 = immobile 5 = wheelchair independent, including corners 10 = walks with help of one person (verbal or physical) 15 = independent (but may use aid eg. cane)	
7. Stairs	0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	
8. Dressing	0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces etc.)	
9. Bowels	0 = incontinent (or needs enemas) 5 = occasional accident (once/wk) 10 = continent	
10. Bladder	0 = incontinent, or catheterised and unable to manage alone 5 = occasional accident (once/wk max) 10 = independent	
	TOTAL SCORE	

Date (dmy): _ _/_ _/_ _ Time: _____ Signature: _____

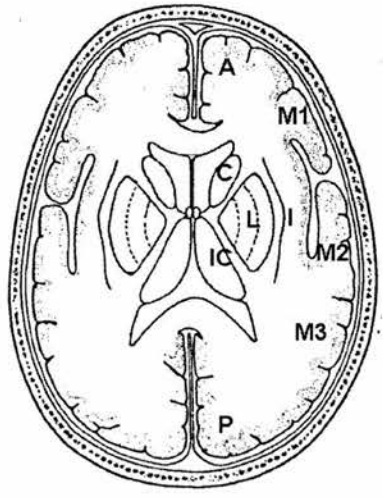
Appendix 5: ASPECTS regions

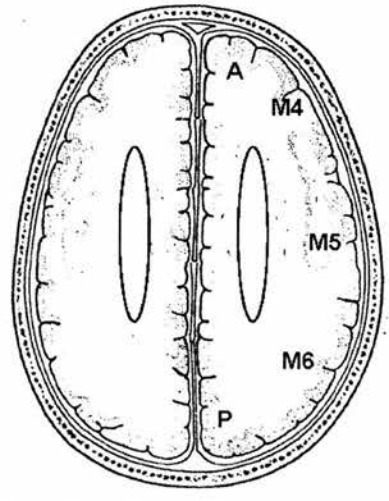
CT SCAN FORM

ASPECTS RATER:_____ PATIENT/SCAN NUMBER = _____

DATE: DDD/MMM/YYYY

SYMPTOM SIDE (OF BODY) = _____ BASELINE/FOLLOW-UP = _____





SCORING THE CT SCAN

	YES	NO
HEMORRHAGE		
TYPE (PH1,PH2, HI1, HI2)		
HMCA SIGN		
HSFBS "DOT" SIGN		
SYLVIAN FISSURE BR SIGN		
ACA LESION		
PCA LESION		
BRAINSTEM/CEREBELLAR		
EYE DEVIATION (L, R, LAEL, LAER, C, NS)		
COMMENTS:		

ASPECT SCORE

SCORE THE ISCHEMIC HEMISPHERE	
1=NORMAL; 0=ABNORMAL	SCORE
CAUDATE	
LENTIFORM	
INSULA	
INTERNAL CAPSULE	
MCA 1	
MCA 2	
MCA 3	
MCA 4	
MCA 5	
MCA 6	
TOTAL (ADD UP)	

HMCA = HYPERDENSE MIDDLE CEREBRAL ARTERY SIGN; HSFBS = HYPERDENSE SYLVIAN FISSURE BRANCH ARTERY SIGN; ACA = ANTERIOR CEREBRAL ARTERY ISCHEMIA; PCA = POSTERIOR CEREBRAL ARTERY ISCHEMIA
EYE DEVIATION: L=LEFT; R=RIGHT; LAEL = LONE ABDUCTING EYE LEFT; LAER = LONE ADBUCTING EYE RIGHT; C=CENTRAL; NS=NOT SCORABLE

SCAN IS OF GOOD QUALITY TO ASSESS ASPECTS: ☐ YES ☐ NO

ECASS 1995 HEMORRHAGE RATING CRITERIA:
HI1 = small petechial along the margins of infarct
HI2 = more confluent petechial within the infarcted volume, without space-occupying effect
PH1 = blood clot not exceeding 30% of infarcted volume with mild space-occupying effect
PH2 = dense clot exceeding 30% of the infarct volume with significant space occupying effect

APPENDIX 6: CT Interpretation Form - Baseline

Patient Initials: _____ **Patient #: FMC**_____ **Exam Date** ___/_____/_____
DD MMM YYYY

Exam # _____ **Start Time:** _____**h**

CTA ❑ **Completed-** ❑**neck,** ❑ **circle of Willis**
❑ **Not Completed**

Symptom Side: ❑ **Right** ❑ **Left** ❑ **Aphasia**

Interpretation by (list name)_____ **Rater** o **1** o **2**

(Tick more than box where relevant, comment where ____)

1. **NCCT quality** ❑ Good–little movement,
❑ Intermediate–some movement,
❑ Poor–majority unreadable due to movement

2. **ASPECTS scoring: Plain CT**
Score 1 for normal or 0 for abnormal:
Only score "acute" lesions on affected side

❑Caudate	❑M2
❑Lentiform	❑M3
❑Insula	❑M4
❑Internal capsule	❑M5
❑M1	❑M6
Total=	

	Yes	No
Hemorrhage		
Type(ph1, ph2, hi1, hi2)		
HMCA sign		
Dot sign		
Swelling/effacement		
>1/3 MCA Territory		
ACA lesion		
PCA lesion		
Brainstem/cerebellar		
Comments:		

Based on NCCT is there evidence of an acute stroke? ❑Yes ❑No
If yes, ❑Anterior Circulation ❑Posterior Circulation

3. **Presence of remote ischaemic change:**

Tick location:

Location	ACA	MCA	PCA	Cbell/brainstem	Small vessel Disease
Right					
Left					

(If CTA not performed stop here; if CTA performed proceed to next page)

Date (dmy): _ _/_ _ _/_ _ **Time:** _____**Signature:** _____

4. **CT Angiography**

APPENDIX 6: CT Interpretation Form - Baseline

❑ Completed -❑neck, ❑ circle of Willis
❑ Not Completed

Quality of CTA scans ❑ Good–little movement, minor venous filling
❑ Intermediate–some movement,
❑ Poor–majority unreadable due to movement/missed bolus

Left						**Right**				
Vessel lumen:	**Normal**	**↓ flow**	**Occl**	**Partial Occl**	**utd**	**Normal**	**↓ flow**	**Occl**	**Partial Occl**	**utd**
ICA	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
If ICA: Cervical	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
Petrous	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
Cavernous	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
Supraclinoid	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
MCA1 proximal	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
MCA1 distal	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
MCA2	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
Distal MCA	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
ACA	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
PCA	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
VA	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
BA	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑

Occl= Occlusion, Partial occl= thrombus or stenosis partially occluding vessel, utd –unable to determine.

Is extra-cranial ICA stenosis present? ❑Yes ❑No

If yes, to what percentage? ❑<50% ❑50-70% ❑>70% ❑Near occlusion

Have you identified an occlusion? ❑Yes ❑No

Blood Pool - Score 1 for normal or 0 for abnormal cerebral blood flow, X for unable to judge. Only score what you consider to be acute lesions on affected side:

❑Right ❑Left ❑bilat (score symptomatic side)

I❑Caudate	❑M2
❑Lentiform	❑M3
❑Insula	❑M4
❑Internal capsule	❑M5
❑M1	❑M6
	Total=❑
Window___ Level___	

Has the CTA changed your level of confidence regarding the presence of an acute stroke?

❑ No ❑ yes – If yes: ❑ Increased confidence in likelihood of stroke
or ❑ Decreased confidence in likelihood of stroke

5. Perfusion ASPECTS – Score 1 for normal or 0 for abnormal cerebral blood flow, X for unable to judge. Only score what you consider to be acute lesions on affected side:
   ❑Right ❑Left ❑bilat (score symptomatic side)

❑Caudate	❑M2
❑Lentiform	❑M3
❑Insula	❑M4
❑Internal capsule	❑M5
❑M1	❑M6
	Total=

Approx MTT delay (main lesion to non-lesion)=_____ms or ❑unable to estimate
In your opinion is there a visible MTT map lesion? ❑Yes ❑No

Based on CTP is there evidence of an acute stroke? ❑Yes ❑No
If yes, ❑Anterior Circulation ❑Posterior Circulation

Date (dmy): _ _/_ _ _/_ _ Time: _____Signature: _____

APPENDIX 7: MRI Interpretation form – Baseline

Patient Initials: _____ Patient VISION#: FMC_____

Exam Date ___/_____/_____ Exam # _____
Symptom Side: ❑ Right ❑ Left ❑ Aphasia

Interpretation by (list name)_____
Date Assessed(D/M/Y) _ _/_ _ _/_ _ _ _

1. DWI: ❑Normal or fill in below:
a) Lesion's: ❑Solitary ❑Multiple
b) Side/s: ❑Left ❑Right
c) Vascular territory/ies involved (4 as many as apply):

Territory	ACA	MCA	PCA	Vertebrobasilar
Left				
Right				

d) Tissue type/s affected? ❑Cortical Grey Matter ❑White Matter ❑Basal Ganglia
❑brainstem nuclei or tracts ❑Cerebellum

e) Age of lesion(s)?
❑hyperacute ❑acute ❑subacute
(hyperacute=no evidence on T2; acute=some T2 & hypointense on ADC; subacute=normalised ADC)

f) **DWI/ADC ASPECTS** – MCA territory Score 1 for normal or 0 for abnormal, X if unable to judge because of scan quality. Do not score remote lesions.

Side rated: If bilateral lesions fill in both rows otherwise rate the affected side

Region	Caud	Lentif	Insula	Int cap	M1	M2	M3	M4	M5	M6	Total
Left											
Right											

2. MRA Circle of Willis:

a) Intracranial Pre-Gd: ❑Normal ❑Abnormal ❑unable poor quality

Site of Occlusion:

Side	ICA	MCA m1	MCA m2	ACA	PCA	Basilar	PICA	Vert
Right								
Left								

b) **Intracranial Post-Gd:** ❑Normal ❑Abnormal ❑unable poor quality
Site of Occlusion:

Side	ICA	MCA m1	MCA m2	ACA	PCA	Basilar	PICA	Vert
Right								
Left								

Site of Stenosis/partial occlusion:

Side	ICA	MCA m1	MCA m2	ACA	PCA	Basilar	PICA	Vert
Right								
Left								

c) Comments (e.g. There appears to be flow beyond a thrombus in the MCA or Decreased signal intensity in MCA but no occlusion seen implying extracranial stenosis)

_____

_____

_____

d) **Hyperintense vessel on FLAIR?** ❑No

Side	ICA	MCA m1	MCA m2	ACA	PCA	Basilar	PICA	Vert
Right								
Left								

3. Neck MRA

Side	Vessel	Normal	Stenosis	Occlusion	State if intra/extra cranial site
Left	ICA				
Right	ICA				
Left	vert				
Right	vert				
	Basilar				

4. a) FLAIR/T2 Are there remote infarcts on these studies? ❑Yes ❑No

Location	ACA	MCA	PCA	Cbell/brainstem
Right				
Left				

b) Small Vessel Disease rating
❑Little ❑moderate ❑large

5. PWI Gradient Echo hypointensities: ❑none ❑solitary ❑multiple

6. Relative perfusion maps

a) rMTT lesion present? ❑Yes ❑No ❑unable quality poor

Vascular territory:

Side	MCA	ACA	PCA	Vert/Basilar
Right				
Left				

b) rMTT ASPECTS – Score acute MTT delay in MCA and not remote infarcts. 1 for normal or 0 for abnormal, X if unable to judge. ❑**Right** ❑**Left**

Region	Caud	Lentif	Insula	Int cap	M1	M2	M3	M4	M5	M6	Total
Aspects											

In event of hyperperfusion with reduced transit time comment _____

c) ❑ MTT>DWI mismatch ❑ DWI=MTT matched ❑DWI>MTT reverse mismatch

d) rCBV: oligemic lesion present: ❑Yes ❑No ❑unable quality
Vascular territory

Side	ICA	MCA	ACA	PCA	Vert/Basilar
Right					
Left					

e) rCBV ASPECTS Score acute CBV changes in MCA. 1 for normal or 0 for oligemia, X if unable to judge and indicate if hyperemia (↑) and/or oligemia (↓) present in each region

❑Right **❑Left**

Region	Caud	Lentif	Insula	Int cap	M1	M2	M3	M4	M5	M6	Total
Aspects											
↑ or ↓											

f) For oligemic regions only: ❑mismatch ❑ matched ❑reverse mismatch

7. a) **Quality of scans:** ❑ Good ❑ Intermediate ❑ Poor
b) If Artefact present: ❑Movement ❑Susceptibility ❑Ghosting ❑Other_____

8. Summary

a) acute/subacute ischaemic stroke seen? ❑Yes ❑No

If no: ❑Normal scan ❑Other pathology_____

b) Suspected etiology: ❑Lacunar ❑central embolic source ❑Carotid atheroslcerosis

❑vertebrobasilar atherosclerosis❑dissection ❑Source indeterminate
❑Other_____

9.Lesion likely to enlarge? ❑Yes ❑No

Appendix 8: Modified Questionnaire for Verifying Stroke-Free Status (QVSFS)

Sum Score: = to 0 (negative- TIA/stroke free), Sum Score between 1-8 (positive– not TIA/stroke free)

o 30 days (+/- 2 weeks)	o 3 month f/u (+/- 2 weeks)	o 6month f/u (+/-2 weeks) telephone	o 1 year f/u (+/- 4 weeks) telephone	o 18 mon f/u (+/- 4 weeks) telephone	o 2 year f/u (+/- 4 weeks) telephone

Since your stroke/TIA:

1. Have you had another stroke or TIA (transient ischemic attack)?

   ❑ Yes ❑ No

   If yes, date: _____

2. Have you had sudden painless weakness on one side of your body?

   ❑ Yes ❑ No

3. Have you had sudden numbness or a dead feeling on one side of your body?

   ❑ Yes ❑ No

4. Have you had sudden painless loss of vision in one or both eyes?

   ❑ Yes ❑ No

5. Have you suddenly lost one half of your vision?

   ❑ Yes ❑ No

6. Have you suddenly lost the ability to understand what people are saying?

   ❑ Yes ❑ No

7. Have you suddenly lost the ability to express yourself verbally or in writing?

   ❑ Yes ❑ No

Yes = 1, No = 0,

Score: _____

Appendix 9: Final Diagnosis and TOAST form

Has the 3 month follow up been completed?
□ If "YES", complete Final Diagnosis and Etiology sections
□ If "NO" explain: □ Patient re-location
□ Unable to contact patient
□ Patient deceased

Final Diagnosis:
□Stroke – □Anterior circulation □ Posterior circulation
□TIA
□Seizure
□Migraine
□Functional
□Other diagnosis_____

If the diagnosis is stroke or TIA, what is the etiology:
□large-artery atherosclerosis
□cardioembolic
□small-vessel occlusion
□stroke of other determined etiology
□stroke of undetermined etiology.

Was carotid endarterectomy performed? □Yes □ No Date:_____

Has the pt had a new cerebrovascular event within the 90day window frame? □Yes □No
□**TIA**
Date of 1st event:_____ Total number of TIA's_____ **OR**
□**Stroke**□ Ischaemic □ Hemorrhagic
Date of 1st event:_____
If new event: □Mild □ Moderate □ Severe
OR
Is this a progression of the original stroke? □ Yes □ No □Can't say
If "Yes", please describe:_____

Other major surgical procedures: □Yes □No If "Yes", please describe:_____
Date:_____

Rater: _____ Signature: _____ Time:_____

Appendix 10 : Patient Initials: _____ Patient #: FMC_____
30day MRI follow up

VISION MRI Interpretation form – 30 day follow up

Patient Initials: _____ Patient VISION#: _____ FMC number_____

30 day Exam Date ___/_____/_____ Exam # _____
Initial day Exam Date ___/_____/_____
Symptom Side: ❑ Right ❑ Left ❑ Aphasia
Interpretation by: _____ Date Assessed(D/M/Y) _ _/_ _ _/_ _ _ _

1. **New discrete DWI lesions** – in comparison to baseline scan.
none ❑
a) Lesion: ❑Solitary ❑Multiple
b) Side/s: ❑Left ❑Right

c) Vascular territory/ies involved (4 as many as apply):

Territory	ACA	MCA	PCA	Vertebrobasilar
Left				
Right				

d) Tissue type/s affected by new lesions?
❑Cortical Grey Matter ❑White Matter ❑Basal Ganglia ❑brainstem nuclei or tracts ❑Cerebellum

e) Age of new lesion(s)?
❑hyperacute (no evidence on T2)
❑acute (some T2 & hypointense on ADC)
❑subacute normalized ADC

2. FLAIR/T2 ASPECTS- of the baseline acute lesion. 1 Normal, 0 abnormal X unable

Region	Caud	Lentif	Insula	Int cap	M1	M2	M3	M4	M5	M6	Total
Left											
Right											

3. MRA Circle of Willis in comparison with baseline:

No occ at baseline or 30 days ❑ or:

Vessel	no recan 0	minor recan 1	partial recan 2	complete recan 3	New occlusion
L ICA					
L MCA					
L ACA					
L PCA					
L Vert					
R ICA					
R MCA					
R ACA					

Appendix 10 : Patient Initials: _____ Patient #: FMC_____
30day MRI follow up

R PCA					
R vert					
Basilar					

4. Based on the MRI is there **hemorrhage**? ❑Yes ❑No
Is it in the original infarct? ❑Yes ❑No

ECASS rating:
❑ HI1 (small petechiae)
❑ HI2 (more confluent petechiae)
❑ PH1 (30% of the infarcted area with some mild space-occupying effect)
❑ PH2 (>30% of infarcted area & significant space-occupying effect; or clot remote from original infarct)

5. Quality of 30 day scans: ❑ Good ❑ Intermediate ❑ Poor
If Artefact present: ❑Movement ❑Susceptibility ❑Ghosting ❑Other_____

6. Summary:
Normal Scan: ❑yes ❑no

If no: ❑ Other pathology_____❑ evolving stroke ❑new stroke

If new stroke:
1. ❑ Normal baseline MRI, new lesion at follow up
2. ❑ New lesion in area of perfusion abnormality at baseline
3. ❑ New lesion not in area of perfusion abnormality at baseline, but in same vascular territory.
4. ❑ Different artery altogether

7. Other pathology or comments please (limit free text)
_____
_____
_____

Appendix 11 : Statement of contribution to work

The collection of data for these imaging studies was carried out between May 2002 and May 2004 in the Department of Clinical Neurosciences in the University of Calgary except for the data in Chapter 7 which was collected before I arrived in the department. In chapter 4, 18 patients were enrolled by physicians from the Departments of Radiology and Neurology, Massachussetts General Hospital, Harvard Medical School, Boston. I was a clinical research fellow employed in this department between August 2001 and March 2004 under the supervision of Dr. Andrew M. Demchuk; subsequently since March 2004 I have been employed as a Neurology resident at the University of Calgary, Alberta, CANADA. I performed all analyses between summer 2003 and autumn 2004.

I organized the overall prospective multimodal imaging study and was project officer on the Canadian Institutes of Health research (CIHR) grant for the study. I designed the consent form and all the data collection forms – follow up, demographics, imaging etc. I also obtained ethical approval for the study. I validated all the clinical data that was inputted into the data base for accuracy and checked all the final diagnoses/TOAST classification for each patient.

At the time of writing there were a total of 298 patients enrolled into the VISION study as a whole. Out of 298 patients I personally enrolled 74 patients and completed follow ups on 85 patients. The rest of the enrolling was completed by my colleagues in the Calgary Stroke Program. This was a prospective cohort study and individual hypotheses were tested independently. There are no sample size calculations in this thesis due to the fact that this was an observational study and was not testing a drug or treatment effect. I also acknowledge the help of the Clinical

trials nurses for their help in maintaining follow up on such a large number of patients. Karyn Fischer RN was key in being a point of contact for patients in follow up. The patients described in Chapter 6 were enrolled into a previous imaging study. I enrolled none of these patients, but developed the hypothesis, analyzed the results and wrote the manuscript.

The projects were chosen in advance and each one was individually analyzed while enrolling continued. This meant that there are differing numbers of patients in each chapter. I planned all the analyses including the statistical analysis. I was responsible for the day to day running of the imaging projects and contacted patients who defaulted from follow up and visited patients in Nursing homes to gather 3 month clinical outcomes.

Appendix 12: Publications arising from this work

Papers

COUTTS SB, Simon JE, Tomanek A, Barber PA, Chan J, Hudon ME, Eliasziw M, Mitchell JR, Frayne RF, Buchan AM, Demchuk AM (2003). Reliability of assessing percentage of diffusion-perfusion mismatch. *Stroke 34:1681-1685.*

COUTTS SB, Barber PA, Demchuk AM, Hill MD, Pexman JHW, Hudon ME, Buchan AM. (2004) Mild neurological symptoms despite middle cerebral artery occlusion. *Stroke 35: 469-471.*

COUTTS SB, Demchuk AM, Barber PA, Hu WY, Simon JE, Buchan AM, Hill MD for the VISION study group (2004). Inter-observer variation of ASPECTS performed in real time. *Stroke* 35:e103.

COUTTS SB, Lev MH, Eliasziw M, Roccatagliata L, Hill MD, Schwamm LH, Pexman WJH, Koroshetz WJ, Hudon MH, Buchan AM, Gonzalez RG, Demchuk AM (2004). ASPECTS on CTA Source Images versus Unenhanced CT Scanning: Added Value in the Identification of Early Ischaemic Changes. *Stroke* 35: 2472-2476.

COUTTS SB, Simon JE, Eliasziw M, Sohn CH, Hill MD, Barber PA, Palumbo V, Kennedy J, Roy J, Gagnon A, Scott JN, Buchan AM, Demchuk AM (2005).Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. Ann Neurol.;57:848-854.

COUTTS SB, Hill MD, Simon JE, Sohn CH, Scott JN, Demchuk AM. For the VISION study group (2005). Silent ischemia in minor stroke and TIA patients identified on MR imaging. Neurology; 65:513-517

Appendix 12: Publications arising from this work

Abstracts

54th American Academy of Neurology Annual Meeting Denver, CO (5/2002)

COUTTS SB, Barber PA, Demchuk AM, Hill MD, Buchan AM (2002) Persistent Ischaemic Attack (PIA): A relapsing resolving stroke syndrome. *Neurology 58 (7)* Supplement 3: A76-A77. Poster

28th International Conference on Stroke and Cerebral Circulation, Phoenix (2/2003)

COUTTS SB, Simon JE, Tomanek AI, Barber PA, Hudon ME, Chan J, Frayne R, Mitchell JR, Eliasziw M, Buchan AM, Demchuk AM (2003). Reliability in assessment of DWI/PWI mismatch. *Poster. Stroke 34: 260.*

55th American Academy of Neurology Annual Meeting, Honolulu, HI (5/2003)

8. COUTTS SB, Simon JE, Tomanek AI, Barber PA, Hudon ME, Chan J, Frayne R, Mitchell JR, Eliasziw M, Buchan AM, Demchuk AM (2003). Is assessment of percentage DWI-PWI mismatch reliable?

Platform. Neurology;60:A515

29th International Conference on Stroke and Cerebral Circulation, San Diego, CA (2/2004)

COUTTS SB, Hill MD, Barber PA, Hu WY, Simon JE, Fischer KL, Buchan AM, Demchuk AM for the VISION study group.(2004) The Alberta Stroke Program Early CT Score (ASPECTS) Performed in Real Time shows good agreement with expert rating. *Poster, Stroke: 35, 266-267.*

Krol AL, **COUTTS SB**, Simon JE, Sohn C, Anderson-Armitage L, Frayne R, Sevick RJ, Eliasziw M, Buchan AM, Demchuk AM, for the VISION study group.(2004) Acute MRI in Speech or Motor Transient Ischaemic Attack Reveals Ongoing

Appendix 12: Publications arising from this work

Ischaemia and Active Disease in a High Proportion of Patients. *Poster. Stroke 35, 261-262.*

World Stroke Congress, Vancouver, BC, Canada (06/2004)

COUTTS SB, Simon JE, Sohn CH, Gagnon AJ, Eliasziw M, Palumbo V, Roy J, Buchan AM, Demchuk AM. For the VISION study group. Nomenclature for using MR as a new lesion surrogate outcome. *Poster. Stroke* 35:e263.

COUTTS SB, Simon JE, Sohn CH, Eliasziw M, Gagnon AJ, Roy J, Palumbo V, Hill MD, Buchan AM, Demchuk AM. For the VISION study group. Minor Stroke and TIA are not benign. *Poster. Stroke* 35: e263.

30th International Conference on Stroke and Cerebral Circulation, New Orleans, LO (2/2005)

COUTTS SB, Simon JE, Sohn CH, Eliasziw M, Hill MD, Barber PA, Palumbo V, Kennedy J, Roy J, Gagnon A, Scott J, Buchan AM, Demchuk AM. Presence of DWI lesion on acute MRI in minor stroke and TIA patients predicts recurrent stroke and clinical outcome. *Platform* (in press).

This work was awarded the Robert G. Siekert New Investigator Award from the American Stroke Association Stroke Council.

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